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Symposium on Infectious Asthma

HYPERSENSITIVITY TO INFECTIOUS AGENTS IN RELATION TO ASTHMA*†

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A SURVEY of the literature indicates that a discussion of infectious asthma must begin by distinguishing between nonimmunologic and immunologic types. The former, which may be defined as the direct result of the pathologic effects of a strategically located infectious process, not accompanied by a state of hypersensitivity, will not be considered further in the present discussion. As Dr. Rackemann has written, "All is not allergy that wheezes." The immunologic type comprises asthma resulting from a state of hypersensitivity to the antigens of infectious agents. Obviously, there can be cases in which the two types are concurrent. Finally, it should be noted that it is customary to exclude from the group of infectious asthmas those cases induced by the inhalation of microbial material, such as fungus spores, to which the individual is hypersensitive. From an immunologic point of view, separation on the basis of the origin of the antigen is not essential; it will not be emphasized here insofar as infectious agents are the source of the provocative antigens.

In addition, the literature leaves one in doubt as to the role of hypersensitivity to infectious agents in the production of intrinsic asthma. There is disagreement as to the diagnostic value of skin tests with bacterial suspensions or antigens and as to whether the immediate or the delayed reaction is the more significant. Some workers have reported excellent results from vaccine therapy; others have had limited success or feel that the results are nonspecific. Exhaustive bacteriologic studies of the respiratory tract have

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revealed a characteristic flora but have not supported the concept of an asthma originating in hypersensitivity to bacterial antigens. The purpose of the present discussion, therefore, is to provide a résumé of allergic responses to infectious agents, as a basis for a reconsideration of their possible significance in the production of intrinsic asthma.

Hypersensitivity to microbial antigens appears in two distinctive forms. During infections, or as a result of vaccination with living or dead bacteria, fungi, or viruses, hypersensitivity may develop with the manifestations typical of anaphylaxis and the Arthus phenomenon, and in many respects similar to those seen in "pollen-type" or "atopic" human hypersensitivity. Because of the large common denominator in these phenomena, it will be convenient to give them a reference term, of which "anaphylactic" type seems to be the most generic. Superimposed upon this state, or frequently without it, there may develop a type of hypersensitivity having distinguishing characteristics. First described in detail by Robert Koch in the form of the reaction now known as the Koch phenomenon in experimental tuberculosis, and most extensively studied in this disease, this type of hypersensitivity is commonly designated as the "tuberculin" type. It is most obvious in the group of processes classified as infectious granulomata, as seen, for example, in tuberculosis and other diseases caused by acid-fast organisms, brucellosis, the mycoses, lymphogranuloma venereum, and probably syphilis. It arises, however, in other types of infection, such as those produced by pneumococci, streptococci, or the virus of vaccinia. For this reason, such terms as "bacterial allergy," and "allergy of infection" have been introduced. Since these terms may properly include the anaphylactic type as well, it is suggested that the phrase "tuberculin type" be retained for historical reasons and for its descriptive value.

The differences between these two types of hypersensitivity should be considered, for they appear to rest upon differences in mechanism that may be significant for the problem of infectious asthma. Basically, the two differ in three respects: (1) the local reaction to the intracutaneous inoculation of the antigen, (2) the constitutional reaction to the intravascular or subcutaneous inoculation of the antigen, and (3) the occurrence of circulating antibody.

In the tuberculin type, on the one hand, the reaction to the intracutaneous inoculation of the antigen is of the delayed inflammatory type accompanied by an indurated swelling that persists for as long as several weeks or more. If the reaction be severe, necrosis and sloughing ensue. In the anaphylactic type, on the other hand, the dermal reaction is the familiar one of the prompt formation of wheal and erythema. If the reaction be severe, there is progressive edema and erythema until hemorrhage and necrosis appear, in other words, the Arthus phenomenon. Rich has pointed out that the fully developed Arthus reaction is indistinguishable from the fully developed tuberculin reaction, but that the developmental processes differ. He suggests that, in the tuberculin type, the reaction is not only delayed but that the necrosis is primarily the result of the destruction of extravascular sensitized cells by

exposure to antigen, whereas in the Arthus type, "death of tissue cells results from vascular damage and ischaemia," the latter enhanced by the edema and by arteriolar constriction. Obviously, a differentiation of the two is not simple.

In the anaphylactic type, the constitutional reaction following parenteral inoculation of the antigen is typically one of acute shock, mediated variously according to the host by smooth muscle spasm, edema resulting from increased capillary permeability, and increased mucosal secretion at strategic sites. There is usually no febrile response. Present knowledge supports the view that these manifestations result from the rapid release by the antigen-antibody reaction of histamine and similar substances. In the tuberculin type, the constitutional reaction to intravascular or subcutaneous inoculation of antigen is delayed and gradually progressive like the dermal reaction. There is characteristically a febrile response. The more severe reactions are said to resemble a transient attack of influenza, and have been accidentally produced in man by inhalation of the vapors rising from boiling solutions of tuberculin. In other words, inhalation of the antigen in these circumstances *did not* provoke asthma. The manifestations are ostensibly the result of a widespread damage of tissue, which is to say that there is no well-defined "shock" tissue. Indeed, there appears to be little knowledge of the physiology of this phenomenon except that it is not mediated by the rapid release of histamine and its congeners, as is the anaphylactic type of constitutional reaction.

Circulating antibody to the provocative antigen is not a significant feature of the tuberculin type, being nondemonstrable by the customary serologic techniques. Positive results have been obtained by the delicate collodion-particle method of Cannon and Marshall. The hypersensitivity cannot be transferred to normal individuals by inoculating them with the serum of sensitive ones. An important amendment to this statement appears to be the recent work of Chase, who succeeded in sensitizing normal guinea pigs by inoculating them with the cellular portion of a sterile peritoneal exudate prepared in tuberculin-sensitive guinea pigs. If substantiated, this work will constitute an experimental proof of the frequently postulated intimate relationship of antibodies and cells in the tuberculin type of hypersensitivity. In contrast, the anaphylactic type is usually readily transferred passively by the serum of sensitive individuals. Indeed, a high level of circulating antibody is requisite for the Arthus phenomenon. Moreover, antibody is usually demonstrable by the ordinary serologic methods in the anaphylactic state due to bacterial antigens.

Up to the present time, sensitization of the tuberculin type has been produced with certainty only by vaccination with intact killed organisms or by actual infection, but not by immunization with isolated antigens of the organism. Sensitization of the anaphylactic type, however, can be produced in all three ways.

Another peculiarity of the tuberculin type is that the local reaction may be provoked in a sensitized individual by the injection of either intact organisms or of antigens isolated from them. In the anaphylactic type, comparable amounts of intact organisms are ineffectual, although the isolated antigens will provoke a reaction.

In the tuberculin type, on the one hand, there is a widespread hypersensitization of tissues, for example, vascular endothelium, cornea, kidney, meninges, lung, and testis, but not smooth muscle. In the anaphylactic type, on the other hand, sensitization seems to be primarily of smooth muscle and vascular endothelium, and possibly of mucous glands. It appears not to be settled whether the increased activity of the latter depends upon sensitivity to antigen, or is secondary to the reaction in the adjacent tissues. Of particular interest is the lack of anaphylactic hypersensitivity of avascular tissue such as the cornea.

The relationship of sensitivity to cells is further shown by the fact that the cells of a host with tuberculin-type hypersensitivity that have so far been tested, namely, spleen, blood leucocytes, and bone marrow, are killed in vitro by contact with the specific antigen. Similar cells from anaphylactically sensitive hosts are not affected by contact with the specific antigen in vitro. Extension of these relationships has been made in studies of tissue cultures initiated with explants from buffy coat, spleen, or testicle: cells from tuberculin-sensitive animals retained their sensitivity for a number of generations and several subcultures, whereas cells from anaphylactically sensitive animals were not affected by contact with antigen, even when there were obvious amounts of antibody in the medium.

Finally, it may be added that eosinophilia and the accumulation of eosinophiles at the site of local reactions are characteristic of the anaphylactic type of hypersensitivity, but appear to be absent in the tuberculin type.

Our present knowledge indicates that all of the phenomena enumerated previously originate in antigen-antibody reactions. The differences are best regarded as variations on a fundamental theme, resulting from differences in the natures of the antigens, of the hosts, and of the host tissues reached by the antigens. There exists, moreover, a borderland of hypersensitive states, such as serum sickness and food and drug allergies, that seem to partake of both of the described types. Nevertheless, although no one of the characteristics discussed is definitive, taken together they form a well-defined pattern. What possible relationship does this pattern have to the question of infectious asthma? Consideration of the physiology of allergic asthma indicates that the bronchial obstruction originates in the three following mechanisms, acting singly or in combination: (1) turgescence of the mucous membranes, representing the effect of edema produced by an increased capillary permeability, (2) increased secretion of mucus and the formation of mucus plugs, and (3) spasm of bronchiolar muscle. Regardless of the existing disagreement as to the relative importance of these three, all of them are characteristic responses in what I have designated as the anaphylactic type of hypersensitivity and not in the tuberculin type. If it be a valid conclusion that the latter is not an important factor in infectious asthma, it would be necessary to reassess the relative diagnostic significance of the early wheal-and-erythema type versus the delayed, tuberculin type of dermal reactions to bacteria and their products. There would also be consequences in respect to the selection of antigens for desensitization.

In conclusion, it should be emphasized that asthma can result from a state of hypersensitivity to microbial antigens, for this is well recognized in the extrinsic asthma produced by fungi. The essential question remains, however, whether or not allergic asthma does in fact occur on a significant scale when the source of the provocative antigen is a focus of infection within the body.

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SURGICAL MANAGEMENT OF INFECTIOUS ASTHMA*†

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THE surgical management of infectious asthma largely resolves itself into the treatment of associated nasal infections. A careful examination of the upper respiratory tract should be carried out in all asthmatic patients, and, whenever disease is found, steps should be taken to eradicate it. These procedures may vary from the local use of vasoconstrictor drugs to complete exploration of all the sinuses. Successful treatment is frequently dependent on the thoroughness with which this is done.

The allergist should be trained in otolaryngologic diagnosis and should keep abreast of the progress in that field. Conversely, the otolaryngologist should be trained in allergic diagnosis and should keep abreast of progress in the allergic field. Both should work in close collaboration if the best results are to be obtained in the treatment of these patients.

Accurate diagnosis is necessary for effective treatment. In order to establish such a diagnosis, the following routine is employed.

EXAMINATION

1. Inspection of the ears, nose, nasopharynx, pharynx, larynx, and teeth, then transillumination of the sinuses.

2. Reinspection and transillumination of the sinuses after vasoconstriction.

3. If pus is noted, it is traced to its source. The maxillary sinus is frequently irrigated for diagnostic purposes. The frontal and sphenoid sinuses are occasionally irrigated.

4. Smears are obtained for cytologic examination and cultures are obtained for bacteriologic study.

5. Roentgenograms are obtained from the four standard angles, and in addition to their diagnostic value they also serve as anatomic maps. A second series of films is frequently made after the injection of iodized oil to study the alterations in the sinus mucosa in more detail.

6. If no complications which need immediate treatment are found, the whole problem may be again evaluated after a period of allergic treatment.

TREATMENT

As a result of this examination appropriate treatment is outlined. Current procedures now employed are:

1. *Acute Rhinitis (the Common Cold).*—Since the virus which causes the common cold activates a host of pathogenic pyogenic bacteria, an effort is made to control this invasion by using a mild vasoconstrictor drug such as 1 per cent

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ephedrine in glucose or saline or 0.25 per cent neosynephrin as a spray, three to four times a day, in order to maintain aeration and drainage and yet not interfere with ciliary activity or normal physiologic processes. Privine has been discarded because of the high percentage of patients who develop a sensitization to the drug and then experience severe secondary nasal congestion after its primary vasoconstriction. Penicillin in saline, 500 units per cubic centimeter, used as a nasal spray every hour during the waking period for two days, then every two to three hours for the next two days, seems to be helpful in shortening the duration of the infectious process.

2. *Subacute Rhinitis (Sphenoethmoiditis).*—In addition to the local treatment employed in acute rhinitis, the Proetz displacement method, using 500 units of penicillin per cubic centimeter or a dilute vasoconstrictor drug, may be used. In either case, polyps resulting from allergic rhinitis are removed, if present.

3. *Acute or Subacute Maxillary Sinusitis.*—Lavage of the maxillary sinuses is carried out by irrigation through the natural ostia whenever infection is suspected. A warm saline solution is used, and 2 c.c. of penicillin, 500 units per cubic centimeter, are injected into the sinus after the completion of the lavage whenever pus is found. Since the majority of these infections are due to penicillin susceptible organisms, the severity and duration of this complication can be materially lessened by this procedure. In a series of eighty cases the number of such treatments necessary to effect a cure was approximately three. Sulfadiazine or penicillin by mouth is also frequently employed, and polyps are removed if present. The secondary associated anterior ethmoiditis usually clears as the infection subsides in the maxillary sinus.

4. ***Acute or Subacute Frontal Sinusitis.***—These infections usually clear under the routine listed previously. Frequently the middle turbinate is fractured medially to obtain better drainage, and occasionally the sinus will be irrigated.

If there are mechanical obstructions in the nose, such as malformations of the septum or middle turbinates, which interfere with normal aeration and drainage and predispose to sinus infections with each cold, they are corrected surgically after the infection has subsided. A submucus resection of the nasal septum or resection of one or both middle turbinates, or both, are done under local anesthesia. The results from these procedures, when indicated, have been excellent, and I have yet to see any harm from either procedure in many hundreds of cases.

The removal of infected and hypertrophied tonsils and particularly adenoids in children is most important in the prevention of these recurrent sinus infections. In the adult, radium or roentgen-ray therapy to the nasopharynx is also helpful when excessive lymphoid tissue is present. Treatment with the roentgen ray is, likewise, frequently employed in persistent subacute ethmoid and maxillary sinusitis, and the results in children are particularly good.

When a persistent allergic rhinitis is present which has resisted both allergic and rhinologic therapy, improvement in aeration and drainage may be obtained by injecting sodium psylliate (Sylnasol) into the submucosa of the turbinates.

Occasionally a window is made into the maxillary sinus under the inferior turbinate in persistent subacute maxillary sinus infections. This procedure seems best justified when we are dealing with penicillin resistant organisms, such as *Bacillus pyocyaneus* and *Bacillus proteus*. In these cases, and particularly in those in which odor is present, the underlying teeth should be examined roentgenographically for apical infection which may extend into the sinus.

5. *Chronic Maxillary Sinusitis.*—The maxillary and ethmoid sinuses are those most frequently found to be chronically infected. If the process is limited to the maxillary and anterior ethmoid sinuses, as revealed by inspection, lavage, and roentgenograms without and with iodized oil injections are done. Nothing is to be gained by conservative treatment. An external operative approach is advocated (Caldwell-Luc operation). This procedure can be done without pain under local anesthesia in a very short time. The principles are, briefly: a short incision, 2 to 3 cm. in length, above the teeth; reflection of the periosteum from the anterior wall of the maxilla; preservation of the infraorbital nerve and vessels; a small opening, 1 to 1.5 cm. in size, into the sinus through the canine fossa; the removal of the infected, polypoid, and degenerated mucosa by gentle curettage; a small window, 1 cm. in diameter, made into the nose under the anterior end of the inferior turbinate; no packing; and closure of the incision with two catgut sutures.

At the same time, the anterior ethmoid cells are exenterated intranasally, if indicated. Penicillin is given intramuscularly both pre- and postoperatively for a few days. Four to five days is the usual period of hospitalization, and healing is usually prompt with little postoperative swelling or discomfort. This procedure has been employed on hundreds of cases with uniformly good results. It is rare indeed that one has further trouble with this sinus after such an operation. The removed mucosa shows cellular degeneration and fibrosis with dilated lymph spaces and polyps. Cellular exudate, bacteria, and frequently small abscesses are noted. These changes are irreversible; hence, complete removal of the mucosa is necessary.

6. *Chronic Ethmoid Sinusitis.*—Chronic ethmoiditis, when associated with infectious asthma, is usually also associated with allergic rhinitis and with chronic infection in other sinuses, particularly the maxillary; less often the sphenoid and frontal sinuses are affected. Polypoid degeneration is present and pus is found throughout its cellular structure. Because of the wide anatomic variation in these cells, intranasal operative procedures are seldom successful in eliminating the disease; and since the other sinuses also present chronic irreversible pathologic changes in the mucosa, an external operative approach is advocated.

The surgical approach is through a small (2 to 3 cm.) curvilinear incision alongside the nose at the level of the inner canthus of the eye. The advantages of this approach are: local anesthesia, control of bleeding by ligation of the anterior ethmoid artery, the complete removal of all ethmoid cells and middle turbinate under direct inspection, and easy accessibility to the sphenoid and frontal sinuses when necessary. The incision is closed in layers, and since none

of the supporting bony structure is removed, there is no deformity and the scar is minimal. Penicillin is used pre- and postoperatively for a few days. There is very little postoperative swelling or discomfort. No packing is required, and the patient can be discharged in from seven to ten days.

When chronic pansinusitis is present, all the sinuses on one side are operated upon at the same time through two incisions, one alongside the nose and one above the teeth. A similar procedure is carried out on the other side seven to ten days later. Analgesia and local anesthesia are usually sufficient. Occasionally pentothal sodium is used intravenously toward the latter part of the operation. Very little after care is necessary, and healing is practically complete in three weeks.

In a series of 128 consecutive cases,[1] first seen by the otolaryngologist and referred to the allergist, external operative procedures were necessary in 13 per cent. This percentage would no doubt be lower in a similar group who first presented themselves to the allergist. However, in either case the percentage is high enough and the minor complications frequent enough to justify close collaboration in the management of these cases.

DISCUSSION

It is a matter of record that sinusitis does frequently occur in asthma and that these patients do improve after the infection has been cleared. The degree and duration of improvement vary widely in published case reports and seem to be directly proportionate to the completeness of the diagnosis and treatment.

There is certainly no reason to advocate conservatism in chronic sinusitis, provided the patient's general condition warrants an attempt to clear his sinusitis. I believe that complete external operation on the advanced cases should be done, and if one had the courage to do the same on the milder cases, perhaps the severe form could be prevented.

The term "complete operation" must not be taken too literally, for, whereas it may eliminate all symptoms in ordinary bacterial sinusitis, in allergic sinusitis, because of the peculiar relationship of bacteria to pathologic changes, it may be absolutely impossible to call it complete, since we still have bone, scar tissue, regenerated membrane, and bacteria present, which may still act as a focus to stimulate the bronchial spasm. This may account for the return of asthma in many cases.

It is wrong to condemn surgery of the sinuses in asthma, for it must be remembered that numerous procedures are classified under this head, from the ill-advised, poorly performed operations to the most carefully executed complete ones, and what may be viewed as adequate at the time of operation may later prove to have been inadequate.

One should not expect to cure asthma by surgery, but rather to attempt to clear up a condition which should be eliminated regardless of asthma, for, by so doing, we can eliminate pain, restore the airway, decrease discharge and toxemia, protect the lungs from chronic changes, and eliminate a focus of infection. If we should also obtain relief from asthma, then we would be doubly rewarded.

In addition to the treatment of the sinuses, otolaryngology offers other aids to the treatment of asthma, such as the instillation of iodized oil into the lung and bronchoscopy by which means cultures may be obtained for vaccines, bronchiectasis and other suppurative conditions may be treated, the presence of bronchial obstruction may be determined, and the acute cases, may be relieved by aspiration.

Finally, I would like to say that I feel that otolaryngology has much to offer asthmatic patients, and that adequate sinus surgery should be employed whenever necessary, for our best results have been obtained by following this procedure in addition to allergic treatment.

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(Symposium to be concluded.)

USE OF ORAL PENICILLIN IN TREATMENT OF BACTERIAL ASTHMA

Preliminary Report*†‡

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SINCE penicillin has become more plentiful, data which point to favorable results in the treatment of chronic infections of the lungs, bronchi, and accessory nasal sinuses are being rapidly accumulated.

Kay and Meade[1] have recently reported excellent results by the intratracheal use of penicillin in chronic bronchitis and minimal bronchiostasis. Some reduction of the signs of toxicity and relief of symptoms in cases with extensive suppuration were also reported by them.

More or less favorable results have been obtained in the treatment of chronic sinusitis[2] by the use of penicillin. Thomas and his co-workers[3] have reported encouraging results in a series of patients with pulmonary infection associated with allergic symptoms.

Since many patients with bacterial allergy are ambulatory, the advent of potent oral penicillin made this antibiotic agent available for use in a much larger group of patients.[4-7]

In a series of cases of bacterial and mixed allergy in which there had been little response to the usual methods of treatment, it was decided to give oral penicillin, with the idea that its antibiotic action might alter the allergenic factor of any susceptible organisms present in the respiratory tract.

The patients selected for study all had partially controlled bacterial or mixed allergic rhinitis and asthma. All but five were having attacks of moderate to severe asthma at the time the treatment was begun. All of the children and seven adults had asthma associated with so-called "acute colds." The age range of this group was from 3 to 84 years. The otolaryngologist found allergic rhinitis and infection present in all of the patients.

In 80 per cent of the patients, x-ray studies were made of the chest and all conditions were diagnosed as sino- or tracheobronchitis. Sinus x-rays showed varying degrees of pathology in 90 per cent of the 25 patients. Bronchoscopic examinations were made on 66 per cent or 18 of the children. Of these, 13 had purulent tracheobronchitis, and five had mucoid secretion in the bronchi. Bronchoscopic examinations were made on only two adults; both had allergic asthma.

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TABLE I. DURATION OF SYMPTOMS

	ADULTS	CHILDREN	TOTAL		ADULTS	CHILDREN	TOTAL
5 weeks	1	0	1	7 years	1	1	2
2 years	2	7	9	8 years	1	1	2
3 years	1	3	4	10 years	0	1	1
4 years	2	4	6	12 years	0	2	2
5 years	1	2	3	30 years	1	0	1
6 years	0	3	3	40 years	1	0	1

All of the patients had previously received the usual types of treatment.

Repeated studies of the nasal flora had been made in most of the cases. The predominating organisms in all were staphylococci and pneumococci—organisms susceptible to penicillin. Of the cultures taken on the day the penicillin was administered, four had changed: one showed *Bacillus proteus* in pure culture, two showed Friedländer's bacillus and one showed *Micrococcus catarrhalis*. The pathogenicity of the staphylococcus was determined by the coagulase test.

The following procedure was carried out in 36 cases:

Penicillin* (Glycillin, buffered penicillin[13]) in tablet form, each tablet containing 20,000 units, was used. Each patient was given 60,000 units every three hours for three days, day and night, or a total of 1,440,000 units. It was thought that this amount would give a satisfactory penicillin blood level[4-8] when administered orally. Except for the first six cases, the penicillin was given one-half hour before a meal or two hours after a meal. Blood levels[14] for penicillin concentration were taken two hours after the first dose in every case, and one hour before the eighth dose in 10 of the adult patients.

In so far as possible, the diet was kept low in fat and low in the less easily digested proteins.

Nasal cultures were taken just before treatment and from three to four weeks after treatment, except in one case in which the culture was taken one week after treatment.

The bacteriologic picture, before and after treatment, reveals two definite facts. All adults who had had pneumococci present before treatment had none after treatment. A very high percentage of staphylococci remained present in the cultures after treatment, but 66 per cent of these were coagulase negative.

The procedures which Miller has employed to date do not indicate whether or not the staphylococci which were found after treatment are the same strains as those which were present before treatment. She proposed that such information might be obtained by use of a method employed by Fisk[10] for the identification of *Staphylococcus aureus* strains by means of bacteriophage. A small series of new cases is being studied by this method.

The entire bacteriologic picture was somewhat changed by the high incidence of upper respiratory infections in the cases studied after the middle of September. This incidence ran parallel with occurrence of colds in the community, especially among the children.

*Glycillin tablets used in this study were supplied by Meta Cine Co., Chattanooga, Tenn. The buffer in this tablet is basic aluminum aminoacetate.

TABLE II. NASAL CULTURES BEFORE AND AFTER TREATMENT IN PATIENTS WHO HAD ASTHMA AFTER TREATMENT

PATIENT	ASTHMA	BEFORE TREATMENT	AFTER TREATMENT
F. S.	M.	*Staph. albus*, coagulase negative; pneumococcus; *Str. viridans*	*Staph. albus*, coagulase negative
S. P.	S.	*B. proteus*	No culture
K. D.	M.	Friedländer's bacillus *(K. pneumoniae)*	Friedländer's bacillus *(K. pneumoniae)*
P. E.	M.	H. *Staph. aureus*, coagulase positive	Pneumococcus
R. U.	M.	*Staph. albus*, coagulase positive; pneumococcus	*Staph. albus*, coagulase negative; *Str. viridans*; pneumococcus
P. H.	M.	*Staph. aureus*, coagulase negative; *H. influenzae*; pneumococcus; *Staph. albus*, coagulase negative	*Staph. aureus*, coagulase negative; pneumococcus
J. F.	S.	*Staph. aureus*, coagulase positive; nonhemolytic streptococcus; *H. influenzae*	*Staph. aureus*, coagulase positive; pneumococcus; *H. influenzae*
W. Z.	S.	*Staph. albus*, coagulase negative; pneumococcus; *H. influenzae*	*Staph. albus*, coagulase negative; *Str. viridans*
J. H.	M.	Friedländer's bacillus; diphtheroids	*Staph. aureus*, coagulase negative; *Staph. albus*, coagulase negative; pneumococcus
F. C.	M.	Lost	*Staph. aureus*, coagulase negative
C. K.	X	Lost	*Staph. albus*, coagulase negative; *Str. viridans*

M. – mild; S. – severe; X – asthma while taking penicillin and since treatment.

It was noted that in several of the cases selected for treatment, *Haemophilus influenzae*, originally absent, had appeared on culture during the course of the study. These organisms persisted. Miller reported that there had been an increase in the presence of *H. influenzae* in the throat cultures studied in the clinical laboratory connected with the hospital of the Woman's Medical College. This indicated that this organism was prevalent in the atmosphere at this season in Philadelphia.

TABLE III. BACTERIOLOGICAL PICTURE OF NASAL CULTURES

ORGANISM	BEFORE TREATMENT			AFTER TREATMENT		
	ADULTS	CHILDREN	TOTAL	ADULTS	CHILDREN	TOTAL
Staph. aureus (Coag. +)	6	13	19	0	5	5
Staph. aureus (Coag. –)	0	3	3	6	10	16
Staph. albus (Coag. +)	0	3	3	0	2	2
Staph. albus (Coag. –)	5	5	10	4	5	9
Pneumococcus (no type)	5	5	10	0	7	7
Pneumococcus (Type 3)	0	1	1	0	0	0
Hemolytic streptococcus	1	0	1	0	2	2
Nonhemolytic streptococcus	3	3	6	0	1	1
K. pneumoniae (Friedländer's)	2	1	3	3	0	3
H. influenzae	1	8*	9	2	5	7
B. proteus	1	0	1	?†	0	0
Str. viridans	1	4	5	0	1	1
B. pyocyaneus	1	0	1	0	0	0
M. catarrhalis	2	1	3	2	2	4
Diphtheroids	2	0	2	2	0	2

*Hemophilus influenzae was apparently a temporary invader.
†No check culture; patient moved away from city.

Two of the patients (adults) who did not respond to treatment showed persistent cultures of Friedländer's bacillus. In the other nine patients, in whom the asthma persisted to a greater or less degree, the bacteriologic cultures before and after treatment varied but revealed no definite consistent changes.

TABLE IV. ORAL PENICILLIN (GLYCILLIN) BLOOD LEVELS

PENICILLIN LEVELS TWO HOURS AFTER FIRST DOSE	ADULTS	CHILDREN	TOTAL	PENICILLIN LEVELS ONE HOUR BEFORE EIGHTH DOSE IN TEN ADULTS	NO.
Less than 0.03	3	2	5	Less than 0.03	2
0.03	7	10	17	0.03	3
0.06	2	7	9	0.06	3
0.12	0	5	5	0.12	2
Total	12	24	36		10

In all but three cases the blood levels[9] were high enough to affect the ordinarily susceptible organism. According to Seager that is a blood level of 0.03.

One of these three patients has had only moderate improvement; the other two, both children, have had no asthma, and one has been not only unusually free from all allergic symptoms, but his general health has also greatly improved.

OBSERVATIONS

The following observations have been made as a result of this study:

1. Bacterial asthma was controlled for a short period of time (six weeks to four months) in 71 per cent of 36 patients given a total dose of 1,440,000 units of oral penicillin. This dose gave a satisfactory penicillin blood level. This result apparently corroborates the findings of Schonwald and Deppe[11] in the series which they recently reported.

2. The nasal cultures taken after treatment showed some apparent changes, the nature and significance of which has not been determined.

TABLE V. RESULTS FOLLOWING TREATMENT

	ADULTS	CHILDREN	TOTAL
Cases treated	12	24	36
No asthma			25
With acute respiratory infection	7	15	
No acute respiratory infection	2	1	
Asthma (mild)			6
With acute respiratory infection	1	3	
No acute respiratory infection	0	2*	
Asthma (severe)			3
With acute respiratory infection	1	2	
Asthma during treatment and following treatment	1	1	2

*Followed playing in piles of leaves.

No definite relationship between the control of the asthma and the bacteriologic picture can be demonstrated to date. The most significant finding was the presence of *Staph. aureus*, coagulase positive, in the cultures before treatment and a similar organism, coagulase negative, after treatment in 66 per cent of the cases showing *Staphylococcus aureus*.

The higher penicillin blood levels had no apparent relation to the change in the bacteriologic picture or to the improvement of the patient. No signs of toxicity or sensitivity to penicillin were noted in this series of allergic individuals.

SUMMARY

1. No definite conclusions can be reached to date, but the findings suggest that further studies are justified.

2. This group of patients should continue under observation for a much longer period; bacteriologic studies should be made at a season of the year when acute upper respiratory infections are not so prevalent.

3. The bacteriologic findings on bronchial as well as nasal secretions should be included in the study. (This work is already under way.)

4. Further studies to determine the most satisfactory dosage of penicillin and the advantage of combining local and oral therapy are being carried out in the cases in this series in which there was no response to the treatment as described.

5. Study of the identity of the staphylococci before and after treatment is being undertaken.

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DISCUSSION

DR. L. TUFT, Philadelphia.—It is quite natural that the newer chemotherapeutic drugs should be tried in patients with a condition as stubborn and unresponsive as so-called "infectious asthma." The sulfonamides were the first to run the gamut of enthusiasm and subsequent disappointment. As far as one could judge, they provided little benefit except perhaps in the prevention or treatment of infectious complications. Penicillin is the latest to joint the ranks of panaceas for asthma, and while some favorable reports have appeared as to its use, our own limited experience with it has been disappointing, up to now. By giving it orally, Dr. Bauman and her associates have improved upon the method of administration, and in that respect their report has value. They have shown that a sufficient amount of the drug gets into the blood to be therapeutically active, so that oral administration can be used instead of the more difficult injection method.

No one can doubt from this or other reports that patients treated with penicillin are benefited somewhat, even though its duration is temporary. However, one must seriously question in this or similar types of treatment whether the beneficial effect can be attributed to the effect of the agent itself or more likely to other measures instituted at the same time. Thus, it is to be noted in the present report that many cases had bronchoscopic aspiration and hospitaliza-

tion, measures which in themselves often relieve these patients. It is exceedingly difficult to establish satisfactory controls when dealing with a condition as capricious as asthma. I might illustrate this by an experience with a patient with severe asthma who recently was in our hospital. He was given large doses of penicillin by injection. Within a short time, the asthma cleared up and he was discharged, free of asthma and without recurrence. It would certainly be easy to attribute the good effect in this patient to the use of penicillin. However, it so happened that this patient had been hospitalized for asthma during exactly the same period a year before. At that time, his symptoms had cleared up with the same degree of rapidity from the same symptomatic measures but without penicillin. In the absence of satisfactory controls and unless better evidence of its efficiency is supplied, one therefore must question the advisability of using penicillin in asthma, except possibly to clear up an infectious complication like pneumonia or suppurative sinusitis. Finally, the fact that penicillin has a beneficial effect cannot be used as a valid argument in favor of the presence of an infectious asthma, since one cannot be certain that the beneficial effect is attributable to the penicillin itself.

Original Articles

CHRONIC TOXICITY OF N'PYRIDYL, N'BENZYL, DIMETHYL-ETHYLENEDIAMINE MONOHYDROCHLORIDE (PYRIBENZAMINE)*†

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SEVERAL potent antihistaminic and antianaphylactic substances have been described recently and their properties have been dealt with in detail in many papers.

Mayer et al.,[1] in 1945, first reported the antihistaminic activity of one of the most potent of these compounds, N'pyridyl, N'benzyl, dimethylethylenediamine monohydrochloride (pyribenzamine). Rennick et al.[2] described the pharmacologic properties of this drug in more detail. They included in their studies many acute toxicologic experiments and they found that the effective dose in animals was many times the toxic dose. This finding made it reasonable to assume that pyribenzamine could be used therapeutically without danger, at least for short periods of time. However, before using it for prolonged periods of time in patients with allergic disorders, it was deemed essential to carry out certain chronic toxicity studies on dogs and human beings.

DOG EXPERIMENTS

Five dogs of the same breed (basset hounds) were used in these experiments. Two of them were given 100 mg. of pyribenzamine orally daily; two of them were given 50 mg. daily for one year, and the remaining dog was not given pyribenzamine. All of the dogs were fed the same maintenance diet of raw horse meat plus percomorph oil.

General Symptoms.—Throughout the twelve-month period of observation all of the dogs remained in good health and exhibited normal activity. At no time was drowsiness or fatigue present. They all showed an appreciable weight gain of 5 to 6 pounds without signs of fluid retention (Table I). The temperature, pulse, and respirations remained normal, and there were no apparent gastrointestinal, neurological, or urinary upsets. Furthermore, the skins of the dogs remained in excellent condition throughout the experiment.

Kidney Function.—There was no evidence of kidney dysfunction throughout the twelve-month period. Frequent urinalyses failed to reveal the presence of albumin or glucose. The centrifuged urinary sediments were all free from red blood cells, white blood cells, or other abnormal microscopic elements. The ability of the kidney to reabsorb water was unimpaired as demonstrated by the

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concentration tests (Table II). Further evidence of unchanged kidney function was shown by the normal blood levels of urea nitrogen (Table III). Blood urea nitrogen as well as creatinine levels were determined at bimonthly intervals and remained within normal limits.

TABLE I. EFFECT OF PYRIBENZAMINE ON BODY WEIGHT (DOGS)

Dog	I	II	III	IV	V
Daily dose (mg.)	50	100	100	50	0
Initial weight (kg.)*	17.7	15.4	15.0	11.8	13.6
Final weight (kg.)†	20.0	18.2	17.7	14.5	16.4

*Initial values were obtained before pyribenzamine was administered.
†Final values were obtained after at least one year of daily treatment with pyribenzamine.

TABLE II. EFFECT OF PYRIBENZAMINE ON THE URINE CONCENTRATION TEST* (DOGS)

Dog	I	II	III	IV	V
Daily dose (mg.)	50	100	100	50	0
Initial specific gravity†	1.040	1.045	1.035	1.020	1.020
Final specific gravity‡	1.050	1.045	1.045	1.040	1.040

*Determined by measuring the specific gravity of urine after withholding fluids for sixteen hours.
†Initial values were obtained before pyribenzamine was administered.
‡Final values were obtained after at least one year of daily treatment with pyribenzamine.

TABLE III. EFFECT OF PYRIBENZAMINE ON BLOOD CHEMISTRY (DOGS)

DOG	DAILY DOSE OF PYRIBENZAMINE (MG.)	BLOOD GLUCOSE (MG./100 C.C.)		BLOOD UREA NITROGEN (MG./100 C.C.)		ICTERIC INDEX		PROTHROMBIN TIME (SECONDS)	
		INITIAL*	FINAL†	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL
I	50	112	98	14	15	<1	<1	7	10
II	100	109	104	17	15	<1	<1	7	10
III	100	86	76	10	15	<1	<1	8	12
IV	50	63	74	11	16	<1	<1	8	10
V	0	83	77	9	15	<1	<1	10	11

*Initial values were obtained before pyribenzamine was administered.
†Final values were obtained after at least one year of daily treatment with pyribenzamine.

Liver Function.—No abnormalities of liver function were detected during the twelve-month trial period. The icteric index, prothrombin time, and blood urea nitrogen were determined bimonthly and all of them remained within normal limits. Values for these tests obtained prior to the administration of pyribenzamine and after twelve months of medication are recorded in Table III. In addition, bilirubin was not found in the urine. Bromsulfalein tests 5 mg. per kilogram were done after the dogs had taken pyribenzamine for eight months and the dye was totally removed from the blood stream of all 5 dogs within one-half hour. This finding plus the unchanged values of the icteric index, prothrombin time, and the blood urea nitrogen indicate that pyribenzamine in therapeutic doses can be administered for prolonged periods without damaging the liver.

Peripheral Blood.—Morphologic studies of the blood and blood cell counts were done after the dogs had received pyribenzamine daily for twelve months (Table IV) and in no instance was granulocytopenia noted. The high hematocrit, hemoglobin, and red blood counts in the control animal as well as the test animals are apparently a characteristic of the breed (basset hound) and in this instance

are not interpreted as abnormal. Careful bone marrow studies will be reported with the rest of the autopsy findings by Becker.[3]

TABLE IV. EFFECT OF PYRIBENZAMINE ON BLOOD ELEMENTS* (DOGS)

Dog	I	II	III	IV	V
Daily dose of pyribenzamine (mg.)	50	100	100	50	0
Hematocrit (% packed red cells)	65	57	66	63	67
Hemoglobin (Gm.)	20.0	18.5	20.0	19.7	20.0
Red blood cells (millions)	10.2	9.4	13.3	12.4	9.2
White blood cells (thousands)	13.7	11.2	11.2	12.3	9.0
Polys (per cent)	63	68	61	59	54

*After one year of daily treatment with pyribenzamine.

TABLE V. EFFECT OF PYRIBENZAMINE ON BLOOD PRESSURE (HUMAN SUBJECTS)

	NORMAL SUBJECTS			ALLERGIC PATIENTS				
	I	II	III	IV	V	VI	VII	VIII
Daily dose of pyribenzamine (mg.)	150	150	150	100	200	200	200	200-400
Days of treatment	80	80	80	275	135	90	60	210
Initial blood pressure (mm. Hg)	130/80	130/80	130/80	104/70	116/68	130/80	138/80	138/88
Final blood pressure (mm. Hg)	130/70	130/80	135/78	120/68	118/76	134/84	140/80	114/82

EXPERIMENTS ON HUMAN BEINGS

Three healthy male subjects, 22, 23, and 24 years of age were given 150 mg. of pyribenzamine daily for eighty days. At no time was their general state of well-being altered and no abnormal objective clinical findings such as significant changes in body weight or blood pressure were noted. In addition, there were no significant changes in the blood pressure of several allergic patients who had taken pyribenzamine for prolonged periods (Table V).

Routine examinations of the urine of the three normal subjects including microscopic examinations of the centrifuged specimens were done weekly throughout the eighty-day trial period, and no abnormalities were detected. Furthermore, there were no significant changes in the urea nitrogen blood levels before and after the trial period (Table VI).

No alteration in liver function was detected. Evaluation of liver function was based on determinations of the icteric index, serum bilirubin, albumin, globin, prothrombin time, and the cephalin flocculation tests. All of these remained unchanged during the course of therapy (Tables VI and VII).

TABLE VI. EFFECT OF PYRIBENZAMINE* ON BLOOD CHEMISTRY† (HUMAN SUBJECTS)

Subject	R.P.	C.B.
Blood glucose (mg./100 c.c.)	105	104
Blood urea nitrogen (mg./100 c.c.)	14	13
Carbon dioxide combining power (volumes per cent)	52	52
Serum albumin (per cent)	4.4	4.2
Serum globulin (per cent)	1.7	1.7

*One hundred fifty milligrams daily for eighty days.

†Values recorded in this table were obtained at end of test period. The values obtained prior to and during the administration of pyribenzamine did not differ significantly from those recorded.

TABLE VII. EFFECT OF PYRIBENZAMINE* ON CERTAIN TESTS INDICATIVE OF LIVER FUNCTION† (HUMAN SUBJECTS)

Subject	R.A.	C.B.	R.B.
Serum bilirubin (mg./100 c.c.)	0.20	0.25	0.30
Icteric index	5	5	5
Prothrombin time (seconds)	12	12	12
Cephalin fluocculation	negative	negative	negative

*One hundred fifty milligrams daily for twenty-one days.

†Values recorded in this table were obtained at end of test period. The values obtained prior to and during the administration of pyribenzamine did not differ significantly from those recorded.

TABLE VIII. EFFECT OF PYRIBENZAMINE* ON THE BLOOD ELEMENTS† (HUMAN SUBJECTS)

Subject	R.A.	C.B.	R.B.
Hematocrit (per cent red cells)	52	48	46
Hemoglobin (Gm.)	15.1	14.8	13.8
Red blood count (millions)	5.2	4.8	4.9
White blood count (thousands)	7.5	7.1	10.0
Polys (per cent)	57	70	58

*One hundred fifty milligrams daily for eighty days.

†Values recorded in this table were obtained at end of test period. The values obtained prior to and during the administration of pyribenzamine did not differ significantly from those recorded.

Complete blood counts, hemoglobin, and hematocrit determinations were done periodically on the three normal subjects and remained within physiologic limits throughout the entire trial period. Similar blood studies were done on six allergic patients who had been treated with pyribenzamine for periods varying from two to eleven months. No changes in the number of red blood cells or granulocytes were noted in the blood of the normal subjects or allergic patients.

SUMMARY

1. Pyribenzamine administered to dogs for a prolonged period (one year) in doses of 50 mg. to 100 mg. daily had no effect on the general behavior of the animals.

2. Furthermore, the drug did not produce a febrile reaction nor did it impair the kidney or liver function. Hematopoiesis was not altered in these animals.

3. Moreover, no chronic toxic changes were noted in the three human subjects who were given 150 mg. of pyribenzamine daily for eighty days. Such limited studies in man, however, are not sufficient as yet to attest to the complete harmlessness of the drug.

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CLINICAL STUDIES WITH N'PYRIDYL, N'BENZYL, DIMETHYL-ETHYLENEDIAMINE MONOHYDROCHLORIDE (PYRIBENZAMINE)*†

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FOLLOWING his classical work on urticarial wheals, Lewis,[1] in 1927, postulated that a histamine-like substance, which he designated H-substance, is liberated by the tissues at the site of the allergic reaction. Since then, it has been the belief of many investigators that H-substance is very closely allied to histamine. With this in mind it is reasonable to assume that an antihistaminic drug might also be antagonistic to H-substance. Thus an antihistaminic substance might prevent or attenuate many allergic reactions.

Only recently have several potent antihistaminic compounds been synthesized and studied. Mayer[2] compared the potency of many of these antihistaminic substances in experimental animals and found N'pyridyl, N'benzyl, dimethylethylenediamine monohydrochloride (Pyribenzamine) to be one of the most potent. In addition pyribenzamine was shown[3] to be nontoxic in many times the effective therapeutic dose. Chronic toxicity studies with pyribenzamine were done on dogs by Koepf, Arbesman and Munafo[4] and no serious toxic effects were noted. Hence, a study of the use of pyribenzamine in the treatment of various allergic disorders in humans seemed justified.

Four hundred ninety-five patients were chosen for study from private practice, the Allergy Clinic of the Buffalo General Hospital, and the Allergy Clinic of the Children's Hospital of Buffalo. In order to insure their cooperation, all patients were seen frequently and given only enough pyribenzamine to last until the next visit. Needless to say, we attempted to be hypercritical in interpreting the effect of pyribenzamine on all of the patients' signs and symptoms. It is obvious that in some instances, because of the many variables that may occur in the course of allergic disorders, difficulties may present themselves in the evaluation of the effect of a drug. Thus, on many revisits, placebos were substituted, and the response was again noted. Substitution of placebos for pyribenzamine helped us immeasurably in evaluating the effect of pyribenzamine and this procedure was repeated several times in the study of most patients.

DOSAGE

The effective dosage of pyribenzamine was found to vary greatly from individual to individual. It also varied in the same patient at different times depending upon his allergic state and the degree of exposure to the offending allergins. The average adult dose varied from 100 to 400 mg. daily, and the dose

*From the Department of Medicine, University of Buffalo School of Medicine, and the Allergy Clinics of the Buffalo General Hospital and the Children's Hospital of Buffalo.

†Furnished through the courtesy of the Ciba Pharmaceutical Company, Summit, N. J.

for children varied from 50 to 200 milligrams. At times, as much as 1,200 mg. of pyribenzamine were given to adults in twenty-four hours without any serious untoward effects. The medication was always given orally and usually in four daily divided doses. Many patients have taken this preparation daily for as long as twelve months without demonstrable effect on blood components, blood pressure, blood chemistry, or urinary constituents.

Pyribenzamine produced relief of symptoms, often within fifteen to twenty minutes. The duration of the effect of this drug showed considerable variation. Some patients reported relief lasting as long as eight to twelve hours, whereas, others had relief for only one to three hours.

EFFECTS OF PYRIBENZAMINE IN THE TREATMENT OF VARIOUS ALLERGIC DISORDERS

The Effect of Pyribenzamine on Constitutional Reactions.—Eight patients were chosen for study who, in the course of routine hyposensitization therapy, had developed repeated constitutional reactions (asthma, wheezing, and urticaria) with a definite dosage of allergen. When 100 mg. of pyribenzamine were given to these patients one-half hour prior to the "shocking dose" no constitutional reaction, either immediate or delayed, developed. The following week the same dosage of allergen was again given to these patients, but without pyribenzamine, and each developed a constitutional reaction.

One patient had repeated generalized reactions to a specified dose of allergen. Thirty minutes after taking 100 mg. of pyribenzamine he was able to tolerate, without reaction, 50 per cent more allergen than formerly. The following week, without pyribenzamine the original smaller dose again produced a systemic reaction.

Studies were done on one anemic patient who developed severe generalized urticaria and angioneurotic edema following injections of concentrated liver extract. She was given 100 mg. of pyribenzamine one hour prior to subsequent injections of the same liver extract. No urticarial lesions followed these latter injections. On one occasion, the injection of liver extract was delayed for over four hours after the ingestion of pyribenzamine. The patient had a recurrence of her urticaria, although not as severe or extensive as when she took no mediation prior to receiving the liver extract.

Effect of Pyribenzamine on Seasonal Allergic Rhinitis (Grasses).—Thirty-four patients with allergic rhinitis due to grass pollen were given pyribenzamine (Table I). Of this number, 24 had had no previous treatment and were seen for the first time during the course of the pollen season with typical symptoms of allergic rhinitis and/or conjunctivitis. Twenty-three of them obtained

TABLE I. EFFECT OF PYRIBENZAMINE ON ALLERGIC RHINITIS—GRASSES

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
No previous therapy	24	23	1	96
Following other unsuccessful therapy	10	7	3	70
Total	34	30	4	88

definite relief and benefit from the drug, that is rhinorrhea, sneezing, nasal occlusion, and itching of the eyes were all diminished. When pyribenzamine was discontinued or placebos were substituted, the symptoms recurred. The remaining 10 patients had had preseasonal treatment without satisfactory relief and hence were given pyribenzamine in addition to their specific hyposensitization therapy. Relief was obtained in 7 cases. Eighty-eight per cent of the 34 patients treated with pyribenzamine had alleviation of their grass hay fever symptoms.

The Effect of Pyribenzamine on Seasonal Bronchial Asthma (Grasses).—Eight of the 34 patients with grass hay fever also had bronchial asthma due to grass pollen. Seven of these 8 patients obtained relief of nasal symptoms when given pyribenzamine, but only 4 had alleviation of bronchial symptoms. Four additional patients who complained of bronchial symptoms but no rhinitis during the grass pollen season were studied. Two of these were relieved. Hence, of a total of 12 patients suffering from bronchial asthma due to grasses, 6 had definite relief from bronchial asthma when given pyribenzamine (Table II).

TABLE II. EFFECT OF PYRIBENZAMINE ON BRONCHIAL ASTHMA—GRASSES

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
Asthma with allergic rhinitis	8	4	4	50
Asthma alone	4	2	2	50
Total	12	6	6	50

The Effect of Pyribenzamine on Seasonal Allergic Rhinitis (Ragweed).—Fifty-seven patients, who had had no previous treatment for their ragweed hay fever were observed during the 1945 ragweed pollen season and treated with pyribenzamine *only*. Of this group 46 (81 per cent) were improved (Table III).

TABLE III. EFFECT OF PYRIBENZAMINE ON ALLERGIC RHINITIS—RAGWEED

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
No previous therapy	57	46	11	81
Following other unsuccessful therapy	49	43	6	88
Total	106	89	17	84

Despite preseasonal or perennial hyposensitization therapy, 49 additional patients with allergic rhinitis due to ragweed pollen developed symptoms during the pollen season. Of this group 43 (88 per cent) had definite relief when given pyribenzamine. Hence, of a total of 106 patients suffering from ragweed pollen hay fever, 84 per cent were benefited by pyribenzamine.

The Effect of Pyribenzamine on Seasonal Bronchial Asthma (Ragweed).—Sixteen of the patients with ragweed hay fever who were treated with pyribenzamine also had seasonal bronchial asthma. Twelve of these obtained relief of nasal symptoms but only in 7 were both nasal and bronchial symptoms alleviated. Two other patients, with ragweed asthma alone, were given pyribenzamine and one was benefited (Table IV).

TABLE IV. EFFECT OF PYRIBENZAMINE ON BRONCHIAL ASTHMA—RAGWEED

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
Asthma with allergic rhinitis	16	7	9	44
Asthma alone	2	1	1	50
Total	18	8	10	44

It was noted that the use of ephedrine and/or aminophylline in addition to pyribenzamine would often control both the nasal and bronchial symptoms better than any one of these drugs alone.

The Effect of Pyribenzamine on Perennial Allergic Rhinitis.—One hundred thirty-eight patients with perennial allergic rhinitis of extrinsic origin were treated with pyribenzamine (Table V). Ninety-three of them had had other methods of therapy such as specific hyposensitization, local therapy, and elimination diets. Despite these various therapeutic measures, these patients still had symptoms of nasal occlusion, sneezing, and rhinorrhea. When pyribenzamine was given in addition to their other treatment, 63 obtained relief. It is interesting to note that the response to pyribenzamine was much better in the group of 45 patients who had had no other previous therapy. Of these 45, 37 showed improvement.

Thirty-five patients with perennial intrinsic allergic rhinitis were also given pyribenzamine. All of these patients had previously had some other therapy without benefit. Seventeen of these 35 patients were definitely improved by this drug (Table VI).

TABLE V. EFFECT OF PYRIBENZAMINE ON EXTRINSIC (NONSEASONAL) ALLERGIC RHINITIS

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
No previous treatment	45	37	8	82
Following other unsuccessful treatment	93	63	30	68
Total	138	100	38	72

TABLE VI. EFFECT OF PYRIBENZAMINE ON INTRINSIC ALLERGIC RHINITIS

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
Previous unsuccessful treatment	35	17	18	48
No previous treatment	0	–	–	0
Total	35	17	18	48

The Effect of Pyribenzamine on Perennial Bronchial Asthma.—Of the 138 patients with perennial extrinsic allergic rhinitis reported previously, 44 also had bronchial asthma (Table VII). Pyribenzamine relieved the asthmatic symptoms of 19 of these. Eighteen additional patients with perennial extrinsic asthma but without rhinitis were also treated with pyribenzamine. All 18 had had previous unsuccessful treatment but their response to pyribenzamine was fairly good. Nine obtained relief. Thus, it should be noted that 28 of the 62 patients with extrinsic bronchial asthma treated with pyribenzamine showed improvement.

TABLE VII. EFFECT OF PYRIBENZAMINE ON EXTRINSIC (OTHER THAN POLLENS) BRONCHIAL ASTHMA

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
Bronchial asthma with allergic rhinitis	44	19	25	43
Bronchial asthma alone	18	9	9	50
Total	62	28	34	45

Three of the 35 patients with perennial intrinsic allergic rhinitis listed in Table VI had bronchial asthma. Although all noted improvement of their nasal symptoms following pyribenzamine, only one reported slight relief of the bronchial symptoms. Three other patients with intrinsic bronchial asthma but without nasal symptoms claimed that pyribenzamine made them worse. Hence, of 6 patients with intrinsic bronchial asthma, only one obtained slight relief from pyribenzamine.

The Effect of Pyribenzamine on Acute Urticaria.—Forty-seven patients with acute urticaria were treated with pyribenzamine and 44 were benefited. Twenty-eight patients had had other forms of therapy without relief and all but three of these improved on pyribenzamine. All of the remaining 19 patients, who had had no other treatment, were benefited by pyribenzamine (Table VIII).

TABLE VIII. EFFECT OF PYRIBENZAMINE ON ACUTE URTICARIA

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
No previous treatment	19	19	-	100
Previous unsuccessful treatment	28	25	3	89
Total	47	44	3	94

TABLE IX. EFFECT OF PYRIBENZAMINE ON CHRONIC URTICARIA

TYPE OF CASE	NUMBER OF CASES	IMPROVED	UNIMPROVED	% IMPROVED
No previous treatment	32	25	7	78
Previous unsuccessful treatment	75	59	16	78
Total	107	84	23	78

*The Effect of Pyribenzamine on Chronic Urticaria.**—One hundred seven patients with chronic urticaria were treated with pyribenzamine (Table IX). Of these patients, 32 had had no previous treatment and, after they received pyribenzamine, 25 had less pruritus, less wheal formation, less edema, and less erythema.

The remaining 75 patients had had various types of therapy in the past without beneficial results. Fifty-nine of these obtained relief from pyribenzamine; among these there were 23 who developed urticaria and arthralgia after penicillin therapy. The skin lesions appeared from three days to three weeks after the penicillin had been stopped. All but one of these patients failed to obtain relief from epinephrine but showed dramatic improvement following pyribenzamine.

*This group also includes patients with angioneurotic edema and dermographism.

The Effect of Pyribenzamine on Miscellaneous Conditions.—Several other ailments were treated without relief. These included migraine, histamine cephalalgia, Ménière's syndrome, dermatitis venenata, psoriasis, and acne rosacea. Several patients with atopic eczema, however, had relief of pruritus and hence improvement of the secondary skin lesions. However, the inadequate number of cases does not permit drawing any significant conclusions at this time.

The Prophylactic Effect of Pyribenzamine on Some Specific Cases.—Three patients, when exposed to cold, would develop urticaria and angioneurotic edema. These cases were all classical examples of physical allergy to cold. Patch tests with ice cubes on all three patients produced typical wheals. When 50 to 100 mg. of pyribenzamine were given to each of these patients one-half hour prior to the patch test, the urticarial wheal failed to develop. Likewise, with continued use of the drug these patients were able to tolerate cold without discomfort. When placebos were substituted for pyribenzamine these patients had a recurrence of symptoms upon exposure to cold.

Two other patients developed marked rhinorrhea, conjunctivitis, and wheezing upon exposure to dogs. This sensitivity was confirmed by marked positive intradermal reactions to dog dander extract and also by repeated exposure to the offending allergen. When these patients were given 100 mg. of pyribenzamine fifteen to thirty minutes prior to exposure to a dog, symptoms were absent or very mild.

Other patients, sensitive to cats, horses, and rabbits developed no symptoms or very mild symptoms upon exposure to their offending allergen after taking pyribenzamine.

One patient, a coffee salesman, was violently sensitive to coffee dust. Whenever he entered rooms of the coffee factory where the concentration of coffee dust was great he developed marked rhinorrhea, sneezing, and conjunctivitis. If he took 50 mg. of pyribenzamine prior to going into the plant, no symptoms whatsoever appeared. Moreover, placebos were ineffective in preventing symptoms.

COMMENT

Side Reactions.—As noted in Table X, 71 per cent of the patients treated with pyribenzamine had no side effects. Only 4.4 per cent of those taking pyribenzamine for various allergic disorders had to discontinue the drug because of the undesirable effects. The most common side effect was sedation. This was manifest usually by drowsiness, fatigue, or an "all gone feeling" (Table XI). In some cases dizziness, faintness, and headache were associated with the sedation. On the other hand, several patients complained of excitability, palpitation, and insomnia. The commonest gastrointestinal disturbance was nausea, occasionally associated with emesis. A few patients had diarrhea, and some complained of dryness of the mouth. One patient developed a dermatitis medicamentosa apparently from the drug, and two patients claimed that they had early menses while taking pyribenzamine.

It is interesting to note that patients receiving large doses of pyribenzamine had side reactions more frequently than those patients receiving small or

TABLE X. SIDE EFFECTS FROM PYRIBENZAMINE

NUMBER OF PATIENTS	NONE	SLIGHT*	MODERATE*	SEVERE†
495	351	92	30	22
Percentage	70.6	19.0	6.0	4.4

*Did not interfere with therapy.
†Pyribenzamine stopped because of severity of side effects.

TABLE XI. SIDE EFFECTS FROM PYRIBENZAMINE IN ORDER OF FREQUENCY

Fatigue and drowsiness Nausea Dizziness Headache	Comprise approximately 95% of all complaints
Dryness of mouth	
Vomiting	
Palpitation	
Nervousness	
Diarrhea	
Perspiration	
Insomnia	
Early menses	
Dermatitis medicamentosa	

TABLE XII. EFFECT OF PYRIBENZAMINE ON ALLERGIC CONDITIONS

(Summary)

TYPE OF CASE	NUMBER OF ALLERGIC CONDITIONS	IMPROVED	UNIMPROVED	% IMPROVED
Allergic rhinitis	313	236	77	75
Bronchial asthma	98	47	51	48
Urticaria	154	128	26	83
Total	565	411	154	73

moderate doses. In many instances these untoward reactions could be circumvented by decreasing to a smaller, but still effective dose. These was also a rather marked difference in individual tolerance to pyribenzamine. Several patients were able to tolerate as much as 1,200 mg. daily without ill effects, whereas in a few others as little as 25 mg. produced undesirable reactions. Many patients having symptoms of drowsiness upon first taking the drug were able to tolerate pyribenzamine without reaction after continued usage. Certain other patients who developed drowsiness from pyribenzamine could prevent this effect by drinking strong coffee shortly after taking the drug.

General Effects of Pyribenzamine in Allergic Patients.—There is no doubt that in allergic patients this drug relieves itching of the skin and reduces urticarial wheals. It also relieves itching of the eyes, rhinorrhea, and nasal occlusion and seems to have some bronchial relaxing effect in asthma. In other words, pyribenzamine often relieves the manifestations of allergic reactions. Furthermore, if given to an allergic patient prior to his exposure to an allergen, pyribenzamine often prevents the occurrence of an allergic reaction.

When the exposure to an allergen was variable, such as during the 1945 ragweed pollen season, it was frequently necessary to adjust the dosage of pyribenzamine in order to afford adequate relief to patients with ragweed hay fever. Usually, when the pollen count was high, larger doses of pyribenzamine

were necessary. Despite adequate dosage of pyribenzamine some patients experienced only partial relief of symptoms. For example, a few patients with typical ragweed hay fever, claiming relief from sneezing, would still have some nasal occlusion.

It was noted by the authors elsewhere[5] that pyribenzamine had very little effect on the results of strongly positive skin reactions. Only the weakly positive reactions (1 plus to 2 plus) were affected. Hence, pyribenzamine was frequently used to keep patients comfortable during diagnostic skin tests.

In bronchial asthma pyribenzamine seems to be more effective prophylactically than therapeutically. This is best demonstrated by those cases in which this drug prevented asthmatic attacks. Yet, once the asthma was present, pyribenzamine did not give the instant and spectacular relief that was obtained with epinephrine.

Inasmuch as it is possible to prevent constitutional reactions due to an overdose of allergen by the administration of pyribenzamine, perhaps only a few injections of huge doses of allergen given just prior to a pollen season could adequately build up the thermostabile antibody titer and hence afford relief of symptoms for an entire season.

The precise mode of action of this drug is unknown; however, it has been shown that it does not prevent the reaction between antigen and antibody in test tube vitro experiments. Other explanations as of its mode of action are that it may act directly as a pharmacologic antagonist or insulator, or that it may act to neutralize the endproduct of the antigen-antibody reaction.

Yonkman has presented evidence[6] that pyribenzamine also has an adrenergic potentiating action. This, he believes, might be due to interference with an enzyme system such as amine oxidase or tyrosinase. This additional action might add to the effectiveness of pyribenzamine in certain allergic disorders.

There is little doubt that pyribenzamine has a definite place in the treatment of various allergic diseases. Many patients in this study experienced marked temporary symptomatic relief. Nevertheless, if permanent relief is to be the therapeutic aim, the etiological factors of allergic manifestations must still be determined and eliminated. In many patients, however, it is impossible to find or eliminate these factors and it is in this group that pyribenzamine is of most value.

SUMMARY

1. Clinical studies with pyribenzamine were done on 495 patients, having a total of 565 allergic manifestations (Table XII).

2. Pyribenzamine relieved sneezing, rhinorrhea, and nasal occlusion in 75 per cent of 313 patients with allergic rhinitis.

3. Pyribenzamine relieved or prevented dyspnea, and cough in 48 per cent of the 98 patients with bronchial asthma.

4. It relieved the pruritus and lessened the degree of erythema and wheal formation in 83 per cent of the 154 patients with urticaria.

5. Pyribenzamine is apparently harmless in effective doses. It has some undesirable, although not serious, side effects.

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STUDIES TO DETERMINE THE ABILITY OF TYROTHRICIN TO SENSITIZE THE SKIN

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TYROTHRICIN, an antibiotic agent first isolated by Dubos[1] in 1939 from cultures of *Bacillus brevis* has been available for experimental and clinical studies since its discovery. The application of penicillin, another antibiotic substance, to clinical medicine is of more recent date. In contrast to penicillin, which has a wide range of usages and several modes of administration, tyrothricin has a limited range of application because of its toxicity under some circumstances. Experimentally, it has been found to produce a hemolytic effect upon red blood corpuscles when administered intramuscularly or intravenously in animals. When given daily in dogs it produced death in from two to eight days.[2] However, it has been found to be safe and nontoxic in human beings when used topically, as in the treatment of body cavities not connected with the circulatory system or in the care of open wounds. Characteristics favoring its use are its stability, a wide range of antibacterial effects, and the fact that its activity is not diminished in the presence of pus, blood, or other tissue fluids.[3] Thus, tyrothricin has been used successfully in the treatment of leg ulcers, mastoidectomy cavities, empyemas, infected wounds, and osteomyelitis[4-8] and in diseases of the eye,[9] nose, and throat.[10, 11]

Inasmuch as tyrothricin is used primarily as a topical agent, the possibility that it may act as a sensitizing substance must be considered. It seemed timely, then, to study this antibiotic substance with a view to determine to what extent it might sensitize the skin of subjects on whom it was being used. It is hardly necessary at this date to call attention to the high incidence of active skin and systemic sensitizations which followed the indiscriminate use of the sulfonamide drugs before any systematic study of these preparations had been undertaken.

The purpose of this study was to determine, first, whether thyrothricin in various concentrations was irritating to the skin and, second, whether sensitivity of the skin could be induced by means of prolonged or repeated topical applications with it. A stock solution of tyrothricin containing 25 mg. per cubic centimeter was employed. Distilled water was added to it to make up solutions containing 1, 2, 5, and 10 mg. per cubic centimeter. These solutions were tested on subjects by means of the standard patch test. Plain filter paper was employed to absorb the solution. Pieces of the filter paper measuring one-half inch square were moistened with the tyrothricin solution in the following manner. Twenty-four pieces were placed on end in a small jar and then 1.0 c.c. of the solution was distributed evenly over the squares. Each piece thereby becoming moderately moist. It was calculated that each square of filter paper contained approximately the following amounts of tyrothricin:

Solution	1 mg. per cubic centimeter	40 μg
	2 mg. per cubic centimeter	80 μg
	5 mg. per cubic centimeter	200 μg
	10 mg. per cubic centimeter	400 μg

Men and women of all ages, who were patients in the general medical and surgical wards, were employed as subjects.* A moistened paper square was applied to the lateral surface of one arm of each subject. It was then covered with an adhesive plaster patch. The latter was removed after an interval of forty-eight hours and the skin examined for evidence of irritation. The treated site was then observed for varying periods of time as indicated in Table I.

TABLE I

STRENGTH SOLUTION (MG./C.C.)	TOTAL SUBJECTS	DAYS OBSERVED AFTER REMOVAL OF TEST							
		0	2	3	4	6	7	8	9
1	20	2		3			7		8
2	59	3	2	3	10	20	6	5	8
5	51	2	3		13	28		5	
10	41		4		19	18			

A total of 171 subjects was tested. A few of these were not seen after the initial inspection. The remainder were observed for periods up to nine days after the original examination. There was no evidence of skin irritation in a single subject.

In the second part of this study the technique for attempting active sensitization was that which was employed by me in earlier studies in experimental sensitization in man with the plant substance, krameria.[12] It was found that the highest incidence of sensitization was achieved when the exciting agent was applied for a prolonged period of time; namely, at least seven days.[13]

A filter paper square moistened with solution of tyrothricin containing 10 mg. per cubic centimeter (400 μg per paper square) was therefore applied to one thigh of each subject, covered by a patch test plaster, and sealed to the skin with a wide strip of adhesive plaster to insure against premature loss of the patch. At the end of seven days the patch was removed and the skin site observed for evidence of any reaction.

Ten men and fourteen women were so treated. After removal of the patch test, each subject was observed two days later, and again at the end of one week. No reaction occurred in any of the subjects. Each person was then requested to report the appearance of any skin irritation at the site of the test application during the ensuing several weeks. No reactions were reported at the end of thirty days. Such a period is usually adequate for the production of active sensitization, since the maximum incubation period is generally considered to be from twenty-one to twenty-eight days.

In one additional female subject immediately after the removal of the seven-day test, another test was applied to an adjacent area of skin for a period of two days. This procedure was repeated each week for three consecutive weeks. She was then observed for two weeks after the fourth and final applica-

*These patients were made available through the cooperation of the various medical and surgical services of the Coney Island Hospital of Brooklyn.

tion. There was no skin reaction to indicate the occurrence of induced sensitivity. Thus, in twenty-four subjects the application of a fairly strong solution of tyrothricin for a seven-day period, and in one patient for a longer time, did not induce sensitivity to tyrothricin.

In addition to a single prolonged application to the skin with tyrothricin, repeated exposures with it at regular intervals were also employed. This procedure was successfully used by me in studies with krameria as an active excitant.[12] In an attempt to simulate the use of tyrothricin clinically in wound dressings, the antibiotic substance was incorporated in small compresses which were fixed to adhesive plaster strips. These are referred to as adhesive compress dressings.* Herrell and Heilman[14-16] determined the optimal therapeutic concentration of tyrothricin, taking into consideration the local tissue toxicity and the maximal antibacterial effect, to be about 500 μg per cubic centimeter. This concentration was employed as the basis for calculating the amount to be incorporated in each gauze compress. Thus, 70 μg were impregnated into a standard gauze pad so that when moistened there was present a concentration of the therapeutic agent of approximately 500 μg per cubic centimeter.

An adhesive compress dressing was moistened with several drops of distilled water and applied to one arm of the subject. To protect against premature loss of the dressing, the latter was reinforced with a wide strip of adhesive plaster. The dressing was removed at the end of three days. If no reaction occurred on the skin, another pad was similarly applied to an adjacent area on the arm on the eighth day following the initial application. This dressing was removed after two days. If no reaction occurred, this cycle was repeated each week until six adjacent areas of skin had been treated. The procedure was not repeated further, since it was felt that there was little likelihood that sensitization would occur beyond this point. In the experiments with krameria, sensitization rarely occurred after the fifth application, and appeared most frequently after two or three treatments.

The technique was altered in a few instances so that the interval between treatments was lengthened to two weeks. In these subjects, four applications were generally made. In several other subjects whose visits could not be regulated, the number of treatments and the intervals between them were not constant.

The subjects employed were patients in the Allergy Clinic.† They generally made visits at intervals of one week. Each patient was instructed to observe the skin following removal of the dressing for evidence of irritation and to mark off the area which had been covered by the pad. This information was presented at the patient's next visit to the clinic. If no reaction was present at the treated skin site, a second compress was applied to an adjacent area of skin. The same skin site was never used twice. The entire procedure was repeated from four to six times as previously noted.

*The adhesive compress dressings were kindly supplied through the courtesy of Johnson & Johnson, of New Brunswick, N. J.

†From the Department of Allergy, Jewish Hospital of Brooklyn.

Twenty-four female subjects were treated six times at intervals of one week. They ranged from 16 to 68 years of age, most of them between 30 and 60 years. Five male subjects ranging from 11 to 34 years of age were treated in similar manner. Each subject was observed from two to four weeks after the final application. There was no instance of active sensitization in any of the twenty-nine subjects in whom this experimental procedure was undertaken.

In addition, four subjects varying from 7 to 50 years of age were given four treatments at intervals of two weeks. In the last group, in whom neither the number of applications nor intervals between them were constant, there were four male subjects from 9 to 61 years of age in whom two, four, five, and six, or a total of seventeen, applications had been made. There were also four female subjects from 13 to 51 years old who were treated six, six, six, and four times, for a total of twenty-two treatments. In both of the latter groups comprising twelve subjects, no evidence of active sensitization was encountered.

Table II summarizes the foregoing findings.

TABLE II

NUMBER OF SUBJECTS	NUMBER OF APPLICATIONS	INTERVAL (WK.)
29	6	1
4	4	2
4	6	1-2
1	5	1-2
2	4	1-2
1	2	3

DISCUSSION

The use of tyrothricin as an antibacterial agent has been almost entirely limited to topical treatment involving the skin (wounds, infections, ulcers) or to the treatment of natural or artificial cavities connecting with the skin surface. This investigation was undertaken to determine whether tyrothricin was irritating to the skin or could sensitize it. Patch test studies in human subjects, with a solution of tyrothricin equal to 10 mg. or 10,000 μg per cubic centimeter, failed to evince any irritative phenomena. This solution is twenty times the concentration recommended as being therapeutically effective. Prolonged application with this solution according to technique successfully employed in other experiments failed to sensitize the test subjects actively. Furthermore, repeated applications of tyrothricin incorporated in adhesive gauze compresses so that the solution thereon was the equivalent of 500 μg per cubic centimeter likewise failed to induce sensitivity. And finally, even though tyrothricin has been available commercially for four or more years, no evidence of clinical sensitivity has been forthcoming thus far.

SUMMARY

1. Within the limits of the described experiments, it can be said that sensitivity to tyrothricin could not be demonstrated.

2. Tyrothricin would appear, therefore, to be a poor sensitizing agent.

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Special Reports

THE GENERAL ADAPTATION SYNDROME AND THE DISEASES OF ADAPTATION*

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(Continued)

COURSE OF THE GENERAL ADAPTATION SYNDROME

The reader is also referred to the sections on "Definition and Terminology" and "History of the General Adaptation Syndrome," where he will find brief sketches of the sequence in which the principal manifestations develop during the general adaptation syndrome.

FUNCTIONAL CHANGES

Probably the most important functional change which occurs in the course of the general adaptation syndrome is the change in *resistance* to damaging agents. It has been found that, if an animal is continuously treated with the same, sublethal, daily dose of one alarming stimulus, its resistance to an additional minimum lethal dose of that same stimulus decreases during the shock phase and gradually returns to, or above, normal in the countershock phase of the alarm reaction. During the subsequent stage of resistance, a considerable amount of specific adaptation to this same alarming stimulus becomes evident; yet, if exposure is continued over a period of many weeks or months, eventually this acquired adaptation breaks down. Apparently, even a fully inured organism cannot indefinitely maintain its adaptation when continuously exposed to a great amount of stress. It is this observation which led to the concept of "adaptation energy." Apparently, under the influence of continuous adaptive work, the adaptability or "adaptation energy" of the organism is eventually exhausted. The time at which this breakdown of adaptation occurs is referred to as the "stage of exhaustion."

The nonspecific resistance is likewise characteristically influenced by the general adaptation syndrome. That is to say, while an animal acquires resistance to a certain agent, its resistance to other agents is also altered. During the shock phase, the nonspecific resistance decreases even more than does the specific resistance. In the countershock phase, on the other hand, there is an increase in the ability of the animal to withstand various types of stress, not only that to which it had been previously exposed. Yet this "nonspecific" or "crossed resistance," is never as great as the specific resistance to the particular agent with which the alarm reaction had been produced.

There are many observations which can best be interpreted as examples of "crossed resistance." Thus, the appendicitis-like changes elicited by certain very acute alarming stimuli may be prevented by pretreatment with the same or different agents.[310] Similarly, the lung edema, normally produced by adrenalin injection, is prevented in animals in which an alarm reaction had previously been elicited either by adrenalin injection or by other agents (e.g., exercise, exposure to cold, surgical interventions, or formaldehyde injections).[552, 561] The anaphylactic shock, produced by reinjection of protein into sensitized guinea pigs, is likewise inhibited during the countershock phase of an alarm reaction evoked by a variety of agents.[236a, 310, 311] Karady and his associates[309]

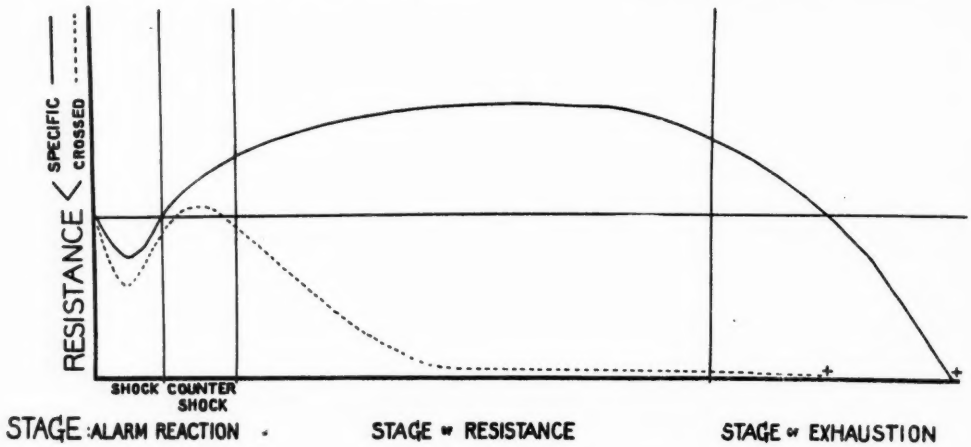


Plate I.—Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the general adaptation syndrome. The progress of time is indicated along the abscissa and the degree of resistance is indicated along the ordinate. Note that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the countershock phase, reaching its maximum during the stage of resistance; in the stage of exhaustion, it falls below normal and, finally, death ensues. Crossed resistance to agents other than that with which pretreatment occurred falls even lower than the specific resistance during the shock phase, rises but slightly during the countershock phase, and is definitely subnormal in the stage of resistance. This indicates that while resistance to one agent (specific) is acquired by pretreatment with this same agent, resistance to other stimuli (crossed resistance) falls below the normal level (horizontal line).

noted, furthermore, that during the alarm reaction the water output is diminished but "if during the course of an alarm reaction produced by any stimulus, the same or any other stimulus is given, the second stimulus not only fails to cause water retention but actually increases urine output. These findings are in good accord with the assumption that two alarm reactions cannot be elicited in rapid succession, and that an alarm reaction produced by one stimulus raises the resistance of the organism both against this stimulus and against any other alarming agent." Several other instances of such an increase in general resistance have been described.[374, 551] Certain types of nonspecific resistance, which were presumed to result from desensitization to histamine, are now also considered as examples of nonspecific tolerance due to the development of an alarm reaction.[677]

It should be emphasized, however, that it is extremely difficult in any one case to prove that "crossed-resistance" is a direct result of the general adaptation syndrome. Undoubtedly, there are other mechanisms which may induce "crossed-resistance." Thus, severe injury to the liver from uranium nitrate may lead to the formation of an atypical hepatic epithelium which is resistant to chloroform.[390] The "crossed-resistance," resulting from the general adaptation syndrome is, on the other hand, probably due to the excessive production of adrenal corticoid hormones, which are known to raise resistance to stress. With our present-day methods it is rather difficult to ascertain the causative mechanism in many instances of crossed resistance.

While during and immediately following the countershock phase nonspecific resistance is increased, the reverse is true during the "stage of resistance." In other words, in animals which have acquired a high degree of specific adaptation against a certain damaging agent as a result of prolonged treatment with it, resistance against other agents is greatly decreased; this presumably means that adaptability or "adaptation energy" is consumed for resistance against one agent.[312, 313, 404, 406, 409, 556]

A particularly interesting new aspect of nonspecific resistance has been discovered recently by Dougherty and his co-workers.[155] These investigators found that, in mice, toxic agents (such as benzene and potassium arsenite) liberate antibodies from lymphocytes, but only in the presence of the adrenals. Dougherty and his associates believe that such alarming stimuli cause the pituitary to produce excessive amounts of adrenocorticotropic hormones, which in turn induce the adrenal cortex to elaborate an excess of corticoids. The latter, through their well-known ability to induce involution of the lymphatic organs, liberate the antibodies from lymphatic tissue. This hormonal mechanism was further elucidated by experiments indicating that purified adrenocorticotropic hormones or adrenal cortex extracts have the same effect upon lymphocytes and antibodies as alarming stimuli. The observations suggest that the alarm reaction may play an important role even in the serologic type of immunity. It has been claimed[63a] also that "the lymphatic tissue acts as a mesenchymal reserve in the simple and immune, local and generalized reactions by furnishing large numbers of lymphocytes which readily turn into macrophages."

The *blood clotting time* shows a pronounced decrease during the alarm reaction,[403] and fibrin formation is markedly accelerated.[130] This is in accord with clinical observations, indicating that, following surgical operations, the platelet count rises[347] while the clotting time decreases. Perhaps the frequent occurrence of thromboses after operations[224] and burns[273] may be due to these changes. Following x-ray treatment, the clotting time also decreases.[466] The *"bleeding time"* is likewise shortened by exposure to damaging agents and, although the mechanism of this change is not clear as yet, increased corticoid production has been considered to be of possible importance.[648-650] According to Ungar[651a] the spleen releases a special hormone-like principle, "splenin," under the influence

of corticoids elaborated as a result of increased adrenotropic hormone production during the alarm reaction. This splenin is held responsible for the reduction of bleeding time. After very serious surgical interventions, however, the blood platelets may disintegrate.[334]

The *blood pressure* rises for a short period immediately after exposure to alarming stimuli. This is probably due to the emergency secretion of adrenalin and has been observed following many types of intervention. After this transitory rise, a period of pronounced hypotention follows, with an eventual return to or above normal during the countershock phase. This response has been studied, especially during surgical shock.[347, 531] Conversely, during the stage of resistance there is a tendency to develop hypertension and nephrosclerosis—especially under certain experimental conditions, to be discussed later.

The *absorption* of various substances, which usually do not pass through the intestinal epithelium in significant quantities, may be greatly increased during the alarm reaction, perhaps because of the intestinal erosions. This has been demonstrated for such compounds as adrenalin and histamine.[553]

Other functional changes are not very conspicuous except for the tachycardia, sweating, peripheral vasoconstriction, and mental stupor characteristic of the shock phase[435] and the total immobility of the pupil occasionally seen after severe trauma.[342]

METABOLIC CHANGES

The *body temperature* decreases during the shock phase of the alarm reaction[126] and this is particularly obvious in adrenalectomized animals.[554] In man, hypothermia is seen after traumas,[435] burns,[273] and other shock-producing agents, while fever is probably a countershock phenomenon.

The *basal metabolism* is decreased by x-ray treatment, while the respiratory quotient is elevated.[305] Systematic animal experiments, performed specifically with the view of determining the effect of the general adaptation syndrome upon the basal metabolic rate, revealed that a variety of alarming stimuli (drugs, surgical interventions, etc.) cause a decrease during the shock phase but, during the countershock phase, the basal metabolic rate returns to normal in spite of continued treatment.[682]

It is of interest in this connection that experiments on sea urchin eggs showed, contrary to expectations, that exposure to damaging agents increases the tissue metabolism; only extremely severe, almost fatal damage results in a decrease. On the other hand, if sea urchin eggs are previously treated with one type of a damaging agent and subsequently exposed to another type, this second exposure tends to cause a sharp decline in tissue metabolism.[74] This may be another example of the decrease in nonspecific resistance at a time when specific resistance became high as a result of pretreatment.

The general adaptation syndrome exerts a very marked effect upon *carbohydrate metabolism*. The blood sugar rises immediately following exposure to an alarming stimulus (''emergency hyperglycemia''). This rise may

still be evident during the peak of the shock phase, especially if the reaction is elicited by abdominal interventions. Later, however, the blood sugar falls, often considerably below the normal level, and, especially in fasted animals, pronounced hypoglycemia may become evident. With the development of counter-shock phenomena, the blood sugar rises again and may reach hyperglycemic levels even if no food is given.[109, 408, 409, 555, 557, 564]

This response is essentially the same no matter what alarming stimulus is used, but, when the stimulus has a specific effect on blood sugar, this is superimposed on that of the alarm reaction. Thus, if the reaction is elicited by muscular exercise, the hyperglycemic peaks are relatively low and the hypoglycemia is especially pronounced, because much glucose is utilized for the muscular work.[563]

In cases of traumatic shock in man, the initial hyperglycemia is very pronounced and prolonged[17, 30, 130, 347, 373, 508, 524, 652] though in some cases the hypoglycemic phase is also well marked.[328] Simultaneously with this rise in blood sugar, the glycogen content of the liver diminishes.[343] In men performing very strenuous muscular exercise it was found that[490] a transitory initial rise is followed by a decrease in blood sugar. Similar glycemic responses have been noted during the "acute malignant or toxic syndrome" of infants[189] following burns,[273, 625] x-rays,[173, 330, 493] and numerous other damaging agents.[380, 619]

Masson[404-406] summarizes his investigations, concerning the variations of the blood sugar during the general adaptation syndrome, as follows: "In rats continuously treated with various damaging agents (exposure to cold, forced muscular exercise, formaldehyde injections), there develops an initial period of hypoglycemia (alarm reaction) followed by a second period of hyperglycemia after a certain degree of adaptation is acquired (stage of resistance). This confirms previous work along these lines indicating that during adaptation to damaging agents certain biochemical changes develop which appear to be entirely independent of the specific nature of the damage and are apparently corollaries of adaptation as such.

"During the alarm reaction, after 24 hours treatment with the above-mentioned damaging agents, a small and perhaps insignificant decrease in the hypoglycemic action of insulin was noted. This was accompanied by a marked increase in the hyperglycemic action of adrenalin and orally-administered glucose.

"During the stage of resistance, after 9 days of treatment, the hypoglycemic action of insulin and the alimentary hyperglycemic response were considerably increased, while the adrenalin sensitivity showed rather irregular changes.

"Comparison of these findings with the existing data concerning the action of acute and chronic damage on the glycemic response to insulin, adrenalin and glucose, shows that changes in the response to these agents cannot be regarded as specific pharmacological actions without considering the possibility that they may merely be the result of adaptation to the non-specific damaging effect of such agents."

In human beings a mild—and rather inconstant—decrease in glucose tolerance was observed under the influence of chronic intermittent anoxia.[80]

In rats, temporary application of clamps to the limbs decreases the glycogen deposition in the liver following carbohydrate ingestion and even insulin fails to improve glycogen storage under these conditions.[250a]

In connection with the changes in carbohydrate metabolism characteristic of the stage of resistance the following observations are of special interest. Contrary to most other damaging agents, exposure to low atmospheric pressure increases the glycogen content of the liver, even in the fasting animal. A rise in the fasting glycogen levels of the liver may also be obtained by treatment with the so-called "carbohydrate active" corticoids. There is good evidence to suggest that adaptation to low atmospheric pressure causes the adrenal cortex to produce an excess of such corticoids which are responsible for the rise in liver glycogen during anoxia. Thus, the adrenal cortex hypertrophies under the influence of low atmospheric pressure and adrenalectomized rats show no rise in liver glycogen when kept in a condition of anoxia.[181-183, 351] All these observations are in agreement with our concept of adrenal response during the general adaptation syndrome. Low atmospheric pressure depresses sugar utilization and—as does any other alarming agent—stimulates the endogenous production of corticoids. It is not unreasonable to assume, therefore, that under the influence of carbohydrate-active corticoids, a large amount of protein is transformed into sugar and that the latter—not being adequate utilized in anoxia—is deposited as glycogen in the liver. The fact that adrenalectomized animals treated with subglycotropic amounts of corticoids also show an increase in liver glycogen during anoxia,[351] is not incompatible with our view, since the factor of decreased sugar utilization would still be operative in them. Perhaps the exceptionally high blood sugar values seen in thyroidectomized animals during the general adaptation syndrome[562] could be explained on a similar basis by assuming that in the absence of thyroid hormone, sugar utilization is also impeded, yet gluconeogenesis from protein is increased, just as in intact animals, as a result of excess corticoid formation. It is more difficult to understand why the "diabetogenic" action of folliculoids—which is inhibited by adrenalectomy—reappears in corticoid-treated, adrenalectomized animals.[295, 299] It is possible, of course (but by no means proved) that the folliculoids could also inhibit sugar utilization.

In connection with what has been said concerning the rise in tissue metabolism under the influence of nonspecific damaging agents, it is noteworthy that some,[424] though not all,[411] investigators believe that during the process of inflammation, protein catabolic processes and gluconeogenesis increase within the area of damage. Severe trauma to one limb results in a pronounced fall in the glucose concentration of the venous blood coming from that limb as compared with the arterial going to it[585]; this likewise supports the view that damaged tissues need more than the normal amount of sugar. Hence, increased gluconeogenesis, due to increased formation of carbohydrate-active corticoids, is

probably a beneficial response to trauma and likely to raise resistance to it. It is not unlikely that the aggravation of diabetes by infections and other types of incidental stress may be due to a temporary, defensive, overproduction of carbohydrate-active corticoids.

The *lactic acid content* of the blood increases rapidly following x-ray treatment,[261, 301, 329] but it has not been definitely established as yet whether or not this is due to an alarm reaction. It is also relevant to mention that the blood sugar and the blood pyruvic acid, as well as the blood and muscle lactic acid, rise following exposure to mechanical trauma in nonadapted animals, while in animals adapted to traumatic injuries these changes are comparatively mild or absent.[451]

The *lipid metabolism* is likewise affected, since marked lipid deposits may suddenly appear in the liver during the course of the alarm reaction.[203, 363, 567] Exposure to low oxygen tension also increases the fat content of the liver.[100] At the same time, the fat tissue itself involutes so that it appears possible that the fat is merely transferred from the fat cells into the liver. The total blood lipids decrease following such stimuli as exposure to low atmospheric pressure.[388]

A decrease in the *cholesterol* content of the blood has been noticed after strenuous exercise,[490] x-ray treatment,[308, 328, 413, 466, 493, 506] in "toxic infants,"[189] following massive hemorrhages,[71] traumatic shock,[33] et cetera. However, the serum cholesterol may remain normal even after exposure to alarming agents sufficiently severe to deplete the adrenal cholesterol stores.[366, 522d]

The *ketone bodies* of the blood increase following x-ray treatment,[685] excessive muscular exercise,[690] and numerous other alarming stimuli.

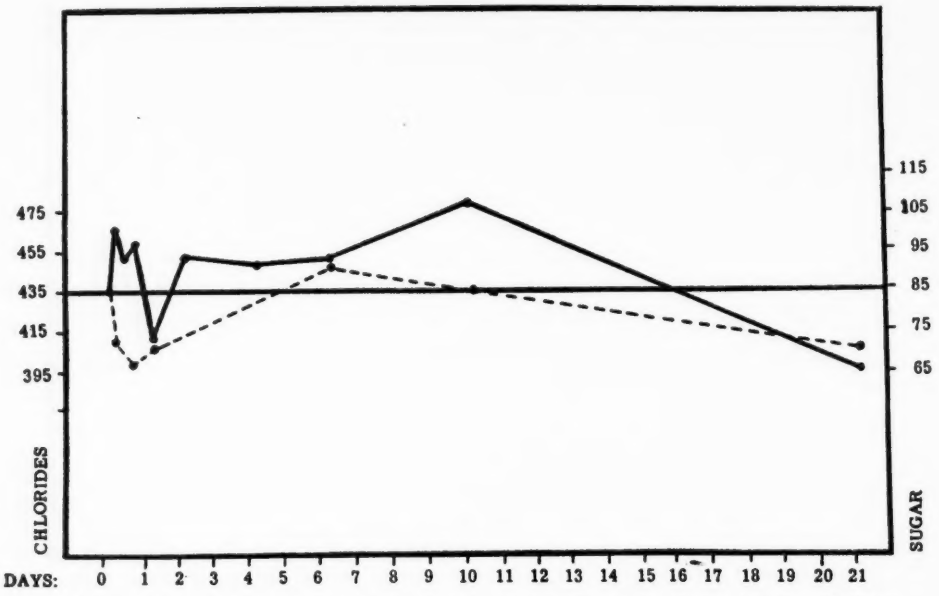
Nitrogen metabolism is severely deranged during the alarm reaction. In the rat there is a pronounced increase in the blood which reaches a peak during the later part of the shock phase.[527] This may explain the increase in total nonprotein nitrogen and uric acid which was noted in man as a result of excessive muscular exercise.[490] In burns,[173] x-ray shock,[493] and surgical shock[451] the nonprotein nitrogen is likewise increased.[163, 520] The same is true of the blood urea,[347, 352] the blood amino acids,[46, 332a] and the blood polypeptides.[117, 347, 352, 379] The nitrogen balance becomes markedly negative during the alarm reaction.[12, 78, 232] Most probably all these changes are due to the marked catabolic effect of the shock phase.

The urinary elimination of creatine is greatly augmented during an alarm reaction produced by cold, exercise, or formaldehyde, but continued treatment with these same agents has no such effect after the symptoms of the alarm reaction vanish. From this, J. S. L. Browne and his associates[79] concluded that the creatinuria observed in many acute conditions is probably due to the resulting alarm reaction.

The globulin content of the blood increases at the expense of its albumin content after burns,[273] traumatic shock,[347] et cetera. It is rather probable that a significant fraction of the protein catabolites, which appear in the blood during the alarm reaction, originates in the lymphatic organs as a result of the lymph tissue-destroying property of excess corticoids.[573] This was made especially probable for the γ-globulin fraction.[155, 156]

The protein catabolic reaction seen during the first phase of the general adaptation syndrome may also have some bearing on the so-called "Donaggio inhibition." The latter is probably due to sudden increase in blood polypeptides and has been considered an index of nonspecific damage following various types of acute diseases and muscular fatigue; hence, it is sometimes also referred to as a fatigue reaction or "Ermüdungsreaktion."[228]

Whole Blood Chloride and Blood Sugar Changes (expressed in mg.%) in the General Adaptation Syndrome of Rats Chronically Exposed to Cold.*



*Selye, H.: Blood Sugar and Blood Chloride Changes in the Alarm Reaction and During Adaptation to Various Stimuli, Arch. int. Pharmacodyn. 60: 259, 1938.

Plate II.—Whole blood chloride and blood sugar changes (expressed in milligrams per cent) in the general adaptation syndrome of rats chronically exposed to cold. In this experiment, the intensity of the cold was such that death ensued after twenty-one days of exposure. The blood chlorides (dotted line) decrease during the first day (alarm reaction) then rise to or even above the normal (stage of resistance) but premortally decline below normal again (stage of exhaustion). The blood sugar changes (solid line) follow essentially the same course, except that during the shock phase (adrenalin hyperglycemia) there is a transitory rise in blood glucose concentration.

Plate III.—Adrenals and lymphatic organs during the alarm reaction. *Fig. 1.* Normal adrenal. Section through the adrenal cortex of a normal rat. Note width of cortex (delimited by arrows) and clear-cut differences between the zona glomerularis and fasciculata. *Fig. 2.* Adrenal in alarm reaction. Section through the adrenal cortex of a rat (similar to that shown in *Fig. 1*) which received toxic doses of formaldehyde, subcutaneously, during forty-eight hours. Note greater width of the cortex, whose cells lost their light, lipid granules. The border between fasciculata and reticularis is no longer distinct. *Fig. 3.* Normal thymus. Low magnification of a cross section through the thymus of a normal rat. Note the light medulla and dark cortical areas. The color of the latter is due to the presence of numerous thymocytes. *Fig. 4.* Thymus in alarm reaction. Cross section through the thymus of a rat (similar to that shown in *Fig. 3*), which received toxic doses of formaldehyde during forty-eight hours. Note the "inversion of the thymus pattern," due to depletion of the cortex of thymocytes and migration of thymocyte debris into the medulla. *Fig. 5.* Naked eye view of adrenal and lymphatic organs of normal rat and during alarm reaction. The thymus (top), two adrenals (middle), and three iliac lymph nodes (bottom) of the normal animal (left), whose thymus is shown in *Fig. 3*, and of the animal during the alarm reaction (right), whose thymus is shown in *Fig. 4*. Note the marked decrease in thymus and lymph node size as well as the increase in adrenal size, accompanied by loss of cortical lipids (brown macroscopic appearance) in the animal killed during the alarm reaction. *Fig. 6.* Thymus in alarm reaction. Higher magnification of an area in the medulla of the thymus shown in *Fig. 4*. Note the well-developed epithelioid thymic reticulum with granular, dark thymocyte nuclear debris. These degenerated thymocyte nuclei migrate towards the medulla and are eventually taken up by the thymic lymphatics.

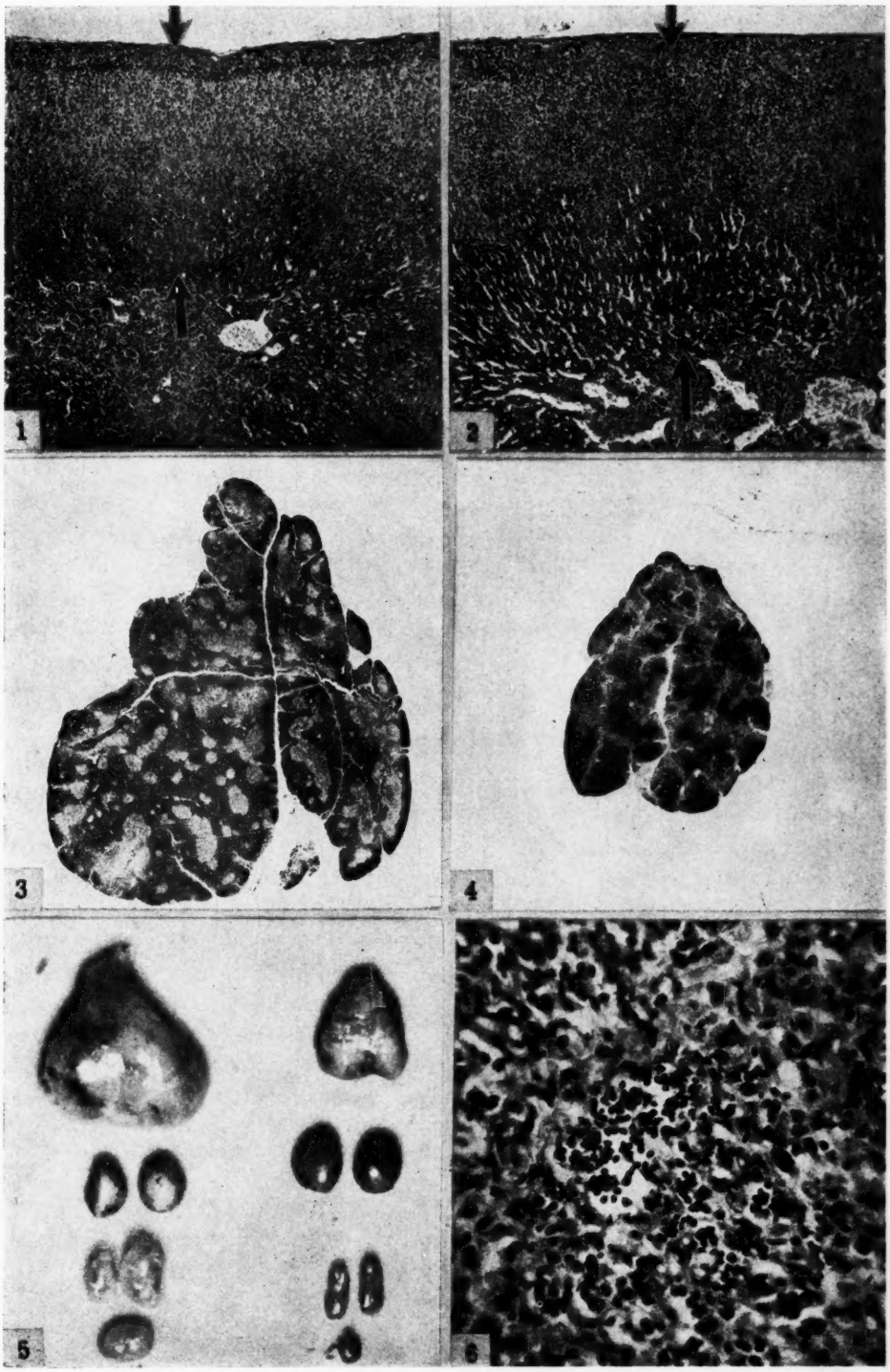


Plate III.—*(For legend see opposite page.)*

A pronounced decrease in blood *chlorides* is one of the most constant changes of the shock phase. It gives way to marked hyperchloremia during the countershock phase.[408, 555, 557] The chloride concentration decreases, particularly in the red cells and less markedly in the plasma.[312, 313] The excretion of chlorides is diminished during the alarm reaction[79] so that the fall in blood chlorides cannot be attributed to a loss through the urine. This receives further support through the observation that bilateral nephrectomy fails to prevent this hypochloremia. The chloride content of the tissues also decreases, with the exception of the tissues of the muscles and the brain, in which it usually increases considerably above the normal level.[569] However, this increase does not account for the decrease in blood chlorides and probably at least a considerable part of them, as well as the organ chlorides, are excreted into the pleural and peritoneal transudates or, if the reaction is produced by trauma, into the traumatized area. This view is in accord with the observation[365] that traumatized muscle tissue is especially rich in chlorides. The high chloride concentration in the subcutaneous edema of the injection region in animals, in which an alarm reaction is produced by formalin, is also in agreement with this concept.[539] The hypochloremia observed in cases of surgical shock,[96, 345, 347, 352, 504] ileus,[652] "toxic infants,"[189] burns,[273] and other types of shock in man, may readily be explained on the same basis. In this respect, excessive muscular exercise again occupies a special position, inasmuch as, contrary to most other agents, it causes an almost immediate hyperchloremia.[557, 563] Perhaps this is due to the fact that countershock phenomena are especially readily elicited by this very physiologic type of an alarming stimulus. More recently it was found that "gravity shock" (seen in rabbits suspended by their ears) causes no change, or a slight fall, in plasma chlorides accompanied by an increase in red cell chlorides.[15]

It appears very probable that the fall in blood chlorides is accompanied by a corresponding decrease in blood *sodium*, especially since such a decrease has been repeatedly observed in cases of shock.[273] Anoxia may cause a temporary rise in the urinary elimination of sodium, followed by a compensatory fall during the countershock phase.[83a]

The *potassium* concentration of the blood rises during the shock phase in burns,[273] ileus,[302] exposure to cold,[386] traumatic shock,[108, 451] muscular exercise,[195] acute infectious diseases,[455, 622] nervous stimulation,[223] et cetera. After trauma there may also be a loss of tissue potassium[108] and an increased excretion of potassium through the urine.[119] Anoxia also tends to raise urinary potassium

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Plate IV.—Thymus during the alarm reaction. *Fig. 1.* Normal thymus. Medium magnification of an area from the thymus shown in Plate III, *Fig. 3.* Note the numerous and regular thymocyte nuclei in the cortical region (lower part of field) and the equally regular but less numerous thymocyte nuclei in the medulla (upper part of field). *Fig. 2.* Thymus in alarm reaction. Medium magnification of an area from the thymus shown in Plate III, *Fig. 4.* Note proliferation of epithelioid thymic reticulum and granular or dustlike debris of degenerated thymocyte nuclei. *Fig. 3.* Thymus in alarm reaction. High magnification of an area from the thymus shown in *Fig. 1.* Note parathyroid-like cell accumulation within the proliferating epithelioid reticulum of the thymus. Surrounding it, there are pyknotic thymocyte nuclei. *Fig. 4.* Thymus in alarm reaction. Higher magnification of an area from the thymus shown in *Fig. 2.* Note the cystlike, epithelioid formation in the center, which may be a dilated Hassall body. Surrounding it there are pyknotic thymocyte nuclei. Pyknosis of the thymocytes and proliferation of the epithelioid elements in the reticulum are particularly characteristic of the alarm reaction.

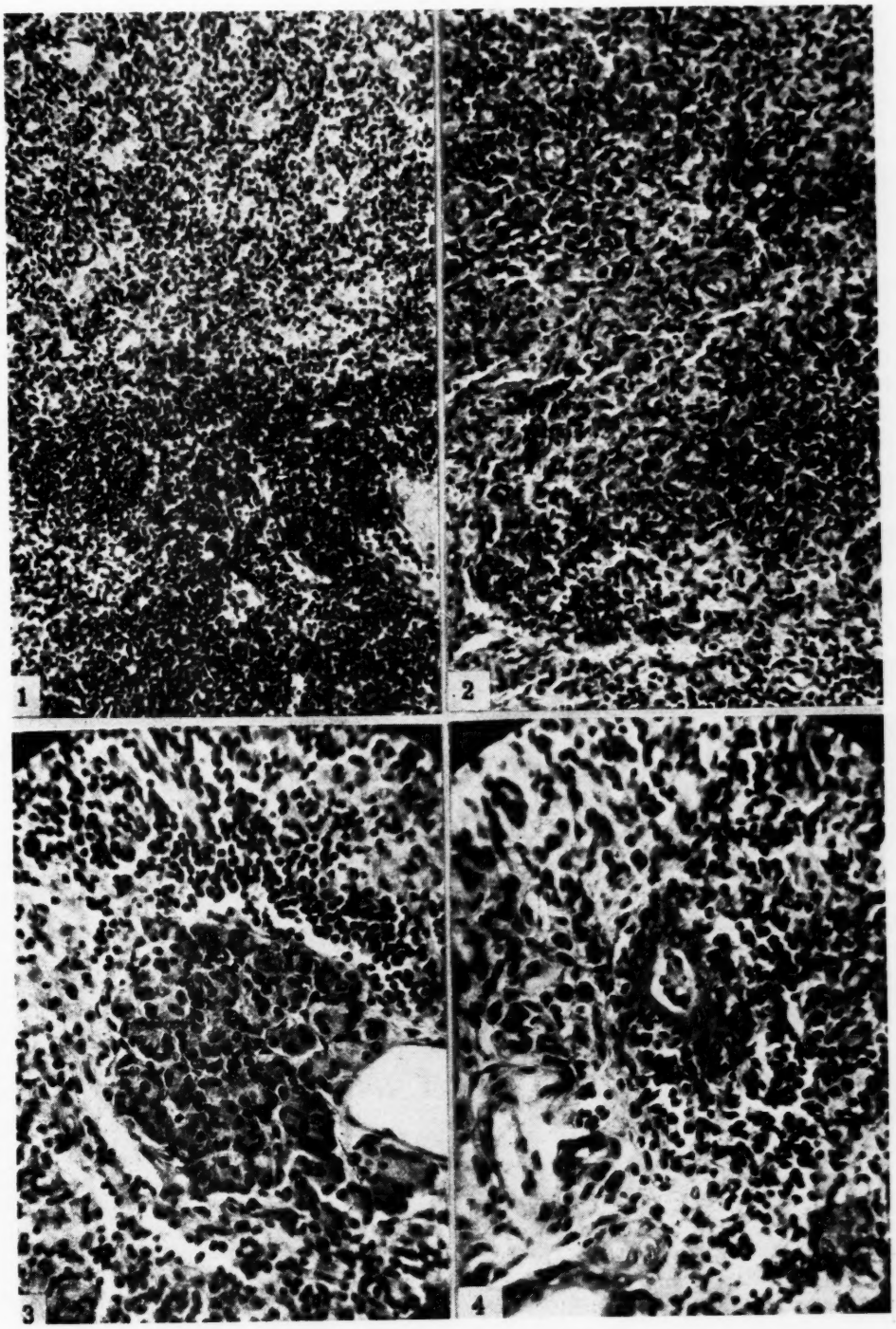

Plate IV.—*(For legend see opposite page.)*

excretion and this is followed by potassium retention in the countershock phase.[83a] It is most probable that the hyperpotassemia, which according to Kendall and Ingle[325] is one of the most important changes in the alarm reaction, is due to the discharge of potassium from the tissues into the blood. In vitro studies indicate that tissue slices also lose potassium under the influence of various "stimulating" or "damaging agents."[75]

The *phosphate* content of the blood is increased during the shock phase and later tends to decrease, even to a point below normal.[410] The hyperphosphatemia

Average White Cell Count During Alarm Reaction Produced by Various Stimuli.*

	Normals	Formaldehyde	Adrenalin	Cold	Surgical Shock	Exercise
RATS						
Total white cell count	13,034	25,264	22,700	22,800	25,800	24,600
Polymorphs	35	76	71	78	84	64
Small Lympho.	58	17	24	14	11	31
Large Lympho.	7	7	5	8	5	5
MICE						
Total white cell count	8,832	18,540	20,010	13,300	17,540	16,800
Polymorphs	38	69	68	68	63	58
Small Lympho.	56	25	26	26	31	33
Large Lympho.	6	6	6	6	6	9

* Harlow, C. M., and H. Selye: The Blood Picture in the Alarm Reaction, Proc. Soc. Exper. Biol. and Med. 36: 141, 1937.

Plate V.—Average white cell count in alarm reactions, produced by various stimuli. Note that both in the rat and in the mouse the total white cell count rises during alarm reactions produced by various damaging agents. This is entirely due to an increase in the number of polymorphonuclear leucocytes and is accompanied by a sharp decrease in small lymphocytes. The large lymphocyte count is not significantly affected.

Plate VI.—Pancreas and stomach during the general adaptation syndrome. *Fig. 1.* Normal pancreas. Macroscopic view of the pancreas of a normal rat. *Fig. 2.* Pancreas in alarm reaction. Macroscopic view of the pancreas of a rat similar to that shown in *Fig. 1*, but having received toxic doses of atropine. Note the distinctly visible white Langerhans' islets along the blood vessels. The pancreatic lobules are atropic and translucent. *Fig. 3.* Pancreas in alarm reaction. Section through the pancreas of a rat, in which an alarm reaction was produced by excessive, forced muscular exercise. Note that acinar tissue remains normal only in a halolike area around the two Langerhans' islets. Here, it contains numerous (eosinophilic) secretory granules. The remaining acinar tissue shows no sign of secretion and is atropic. (Selye: Studies on Adaptation, Endocrinology 21: 169, 1937.) *Fig. 4.* Pancreas in experimental periarteritis nodosa. The lesion was produced by desoxycorticosterone acetate overdosage in the rat. Note marked hyalinization of the perivascular connective tissue with round-cell infiltration, presumably a late stage of periarteritis nodosa in which scar formation has become prominent. *Fig. 5.* Normal stomach (right) with proventriculus in the lower and gastric mucosa in the upper part of the field. Stomach in alarm reaction (left). Alarm reaction produced by transection of the spinal cord, below the seventh vertebra in a rat killed nineteen hours after the intervention. Note that the proventriculus remains unchanged, but the gastric mucosa is hyperemic and contains numerous deep ulcers covered with dark blood clots.

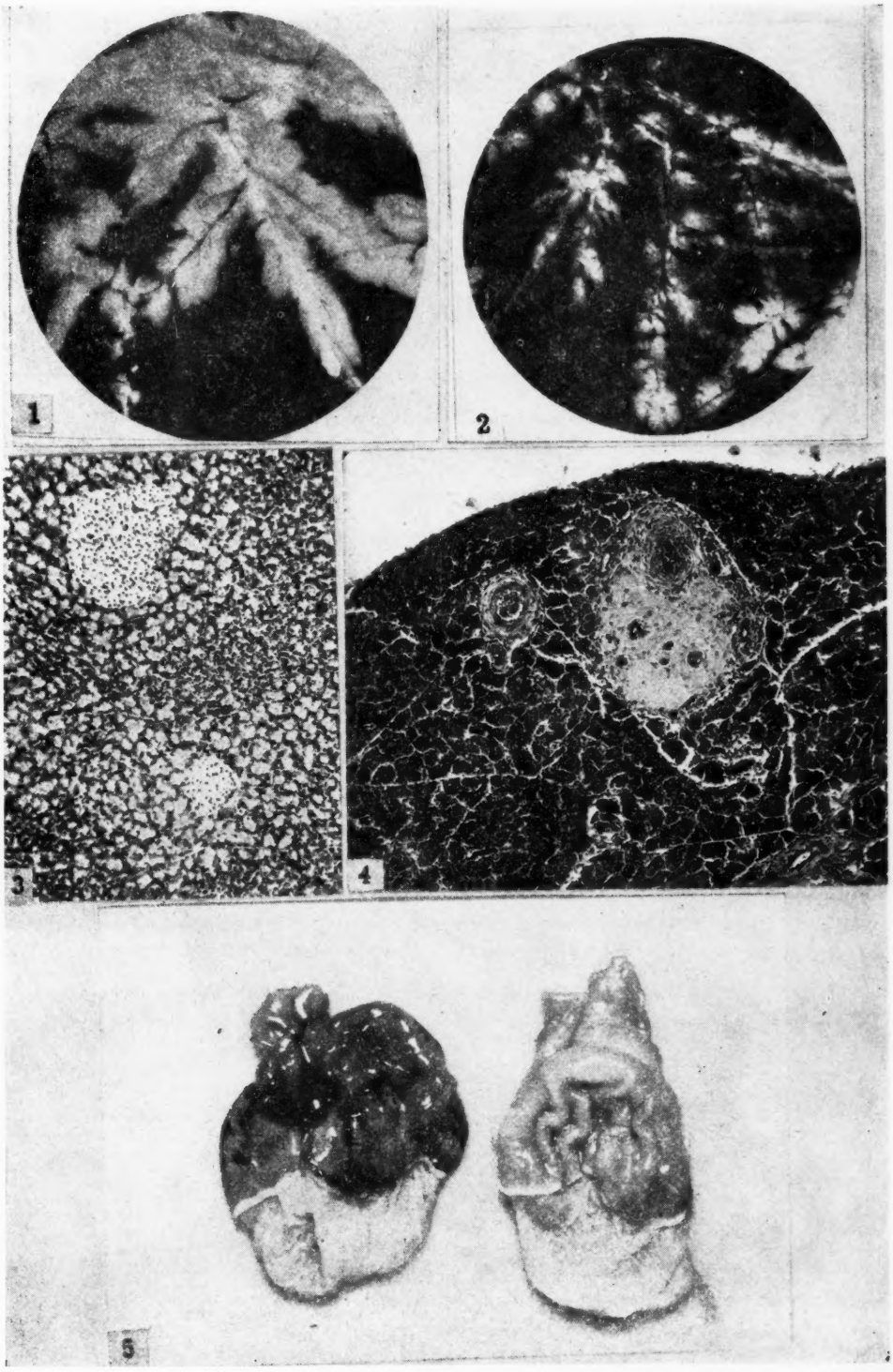

Plate VI.—*(For legend see opposite page.)*

of the shock phase may be due to the liberation of phosphorus from catabolized tissues.[108] The phosphatemic curve, as described earlier, agrees with that observed following massive hemorrhages,[457] asphyxia,[456] traumatic shock,[451] "gravity shock,"[15] deep anesthesia,[397] muscular exercise,[247, 481] and histamine injections.[97] During recovery from shock there is phosphaturia.[15]

The *blood volume* is greatly decreased in animals during the shock phase but rises above normal during the countershock phase.[312, 313] While the decrease in blood volume during shock caused by trauma,[62, 269, 347, 435, 436] x-rays,[173, 438] burns,[348] etc., is well known to clinicians, the secondary blood dilution of the countershock phase has not as yet been adequately studied in man.

Diuresis is diminished in the shock phase but rises above normal during or immediately after the countershock phase.[79, 83a, 285, 286, 309]

The *blood pH* has not been studied as yet with the view of determining its variations throughout the adaptation syndrome, but clinical evidence at hand indicates that, in surgical shock,[91, 115, 263-265, 347] burns,[273] gas gangrene,[695] "gravity shock,"[15] deep anesthesia,[136] and other conditions capable of eliciting the shock phase, marked acidosis occurs. The observation that the acute acidosis produced by radium and x-ray treatment or peptone injections is followed by an alkaline wave[248, 276, 338, 340, 341, 493, 658] makes it very likely, however, that the acidosis of the shock phase is reversed during the countershock phase.

Enzymatic activities probably play a prominent role in the catabolic phenomena which occur during the alarm reaction.[651a] Thus it was found that following a burn or trauma to a dog's extremity, the peptidase activity rises abruptly in the lymph draining from the affected area. In the calf and rat an increase in this enzymatic activity of the serum has consistently been found following a burn.[695a] The view has repeatedly been expressed that injured tissue produces proteolytic enzymes[424a, 430a] and studies on fibrinolytic enzymes lead to the view "that pathological syndromes associated with cellular injury, from any cause whatsoever, might be the effect of the release of toxic by-products of proteolysis from the action of this enzyme."[616a]

The effects of the general adaptation syndrome on *hormone metabolism* will be discussed in the section dealing with the endocrine theory of the syndrome.

Plate VII.—Liver and kidney during the general adaptation syndrome. *Fig. 1.* Normal liver. Naked-eye view of the liver of a normal rat. *Fig. 2.* Liver in alarm reaction. Naked-eye view of the liver in a rat in which an alarm reaction was elicited by exposure to cold. Note the light color of the hepatic parenchyme due to marked fatty infiltration. Formation of fatty livers is a comparatively uncommon accompaniment of the alarm reaction. *Fig. 3.* Normal kidney. Medium magnification of a section through the kidney of a normal rat. *Fig. 4.* Experimental nephrosclerosis produced by desoxycorticosterone acetate overdosage in the rat. Note greatly enlarged glomerulus with transudation of hyaline material into the capsular space and dilated convoluted tubules, many of which contain hyaline casts. A medium-sized arteriole (arrow) shows hyaline necrosis of its walls. *Fig. 5.* Experimental renal infarct produced by desoxycorticosterone overdosage in the rat. Note sclerosed infarct area (right) and comparatively normal renal tissue (left). (*Figs. 3, 4,* and *5* taken from Selye and Pentz: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. 49: 264, 1943.) *Fig. 6.* Experimental nephrosclerosis produced with desoxycorticosterone acetate in the monkey. Note that the afferent arterioles of several glomeruli are almost completely hyalinized (arrows), and many of the dilated tubules contain hyaline casts.

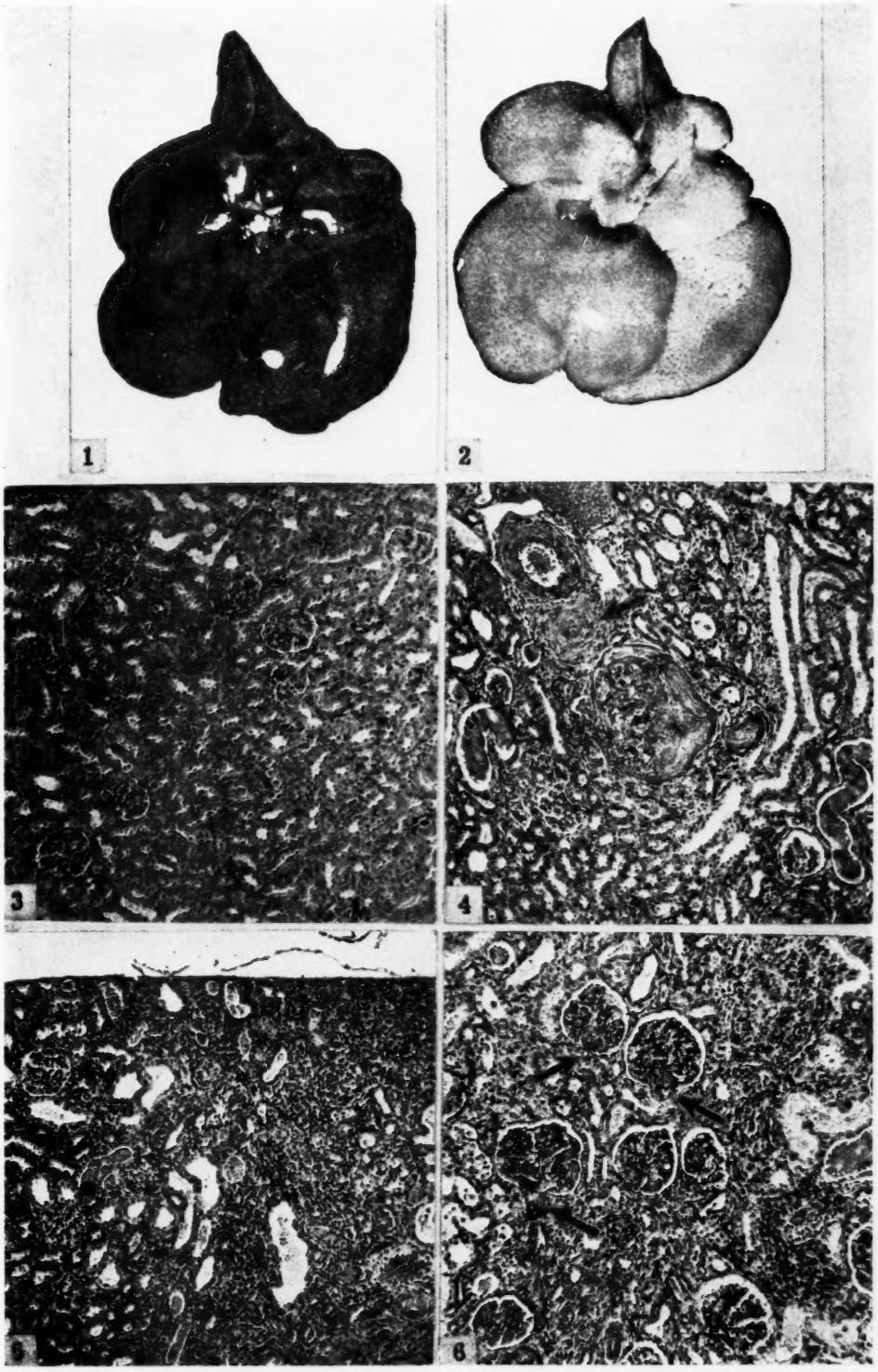

Plate VII.—*(For legend see opposite page.)*

PATHOLOGIC ANATOMY

One of the most important morphologic changes in the alarm reaction is the enlargement of the *adrenal cortex*. Its individual cells hypertrophy and discharge their lipid granules. This has been considered a sign of increased endocrine activity. True hyperplasia is usually less pronounced. These changes take several hours to develop and, as a rule, do not reach their peak until countershock phenomena are evident.[545] The adrenal changes, and especially the rather characteristic lipid distribution pattern in the cortex during the three stages of the adaptation syndrome, have repeatedly been described.[129, 131, 152, 698] The cholesterol content of the adrenal cortex rapidly decreases under the influence of alarming stimuli.[366, 522d] It appears that the cortical hypertrophy and lipid loss of the alarm reaction subside quite regularly during the stage of resistance but reappear during the stage of exhaustion.

The chromaffin granules of the medulla are discharged within a few minutes after exposure to an "alarming stimulus," and the medullary cells become vacuolized. In certain extremely acute cases, adrenal hemorrhages and bilateral necrosis of the medulla were observed. This is noteworthy because it may explain why the adrenal medulla is so often predisposed to become the site of blood-borne infections.[545] It will be seen later that in addition to these morphologic changes there is a great deal of other evidence showing that the adrenals play an important part during alarm reaction and secrete adrenalin immediately after exposure, even before the shock phase is evident, while corticoid secretion is a countershock phenomenon.

The adrenal changes are essentially the same, irrespective of the alarming stimulus used, and have been observed in the rat,[541, 543, 545] in the rabbit,[402] and in the guinea pig.[203] Previously, these lesions have been described often as the specific result of burns,[195b, 273] infectious diseases,[9, 29, 141, 398, 448, 478, 518, 635, 636] intoxication with various drugs,[147, 394, 523, 678] bacterial toxins,[464] x-rays,[214, 282, 482] ultraviolet rays,[237] et cetera. Now it is increasingly recognized, however, that the cortical hypertrophy occasioned by the alarm reaction is responsible for the adrenal enlargement which ensues after exposure to such diverse stimuli as

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Plate VIII.—Hormonally produced renal lesion similar to those occurring in diseases of adaptation. *Fig. 1.* Experimental nephrosclerosis produced with desoxycorticosterone acetate in the rat. Note numerous distended tubules, some filled with hyaline casts. The arrow points to an enlarged hyalinized glomerulus. *Fig. 2.* Prevention of nephrosclerosis by ammonium chloride. The rat whose kidney is shown here was treated with desoxycorticosterone acetate in the same manner as that whose kidney is represented in *Fig. 1*, however, it was simultaneously given ammonium chloride solution to drink. Note absence of pathologic changes. (Selye, Hall, and Rowley: Prevention of Experimental Nephrosclerosis With Ammonium Chloride, Lancet **248**: 301, 1945.) *Fig. 3.* Experimental interstitial nephritis produced with lyophilized anterior pituitary substance in a rat receiving a high sodium chloride intake. Note leucocytes between the tubules. *Fig. 4.* Experimental interstitial nephritis. Higher power view of inflammatory cells between tubules of the kidney shown in *Fig. 3*. *Fig. 5.* Experimental nephrosclerosis produced with lyophilized anterior pituitary material and high sodium chloride intake in the rat. Note greatly dilated tubules, some with casts and transudation of hyaline material into the capsular space. *Fig. 6.* Experimental nephrosclerosis. Another area of the kidney shown in *Fig. 5*. Note hyalinization of afferent arteriole, near its junction with glomerulus (arrow), enormously enlarged glomerulus with transudation of hyaline material into the capsular space. *Fig. 7.* Prevention of experimental nephrosclerosis with ammonium chloride. The rat whose kidney is shown here was treated in the same manner as that whose kidney is represented in *Figs. 3, 4, 5*, and *6*, however, it was simultaneously given NH_4Cl solution to drink. Note that pathologic changes are completely prevented. (*Figs. 3, 4, 5, 6*, and 7 taken from Hall and Selye: Prevention of the Nephrosclerosis Usually Induced by Anterior Pituitary Extract, Rev. canad. de biol. **4**: 197, 1945.)

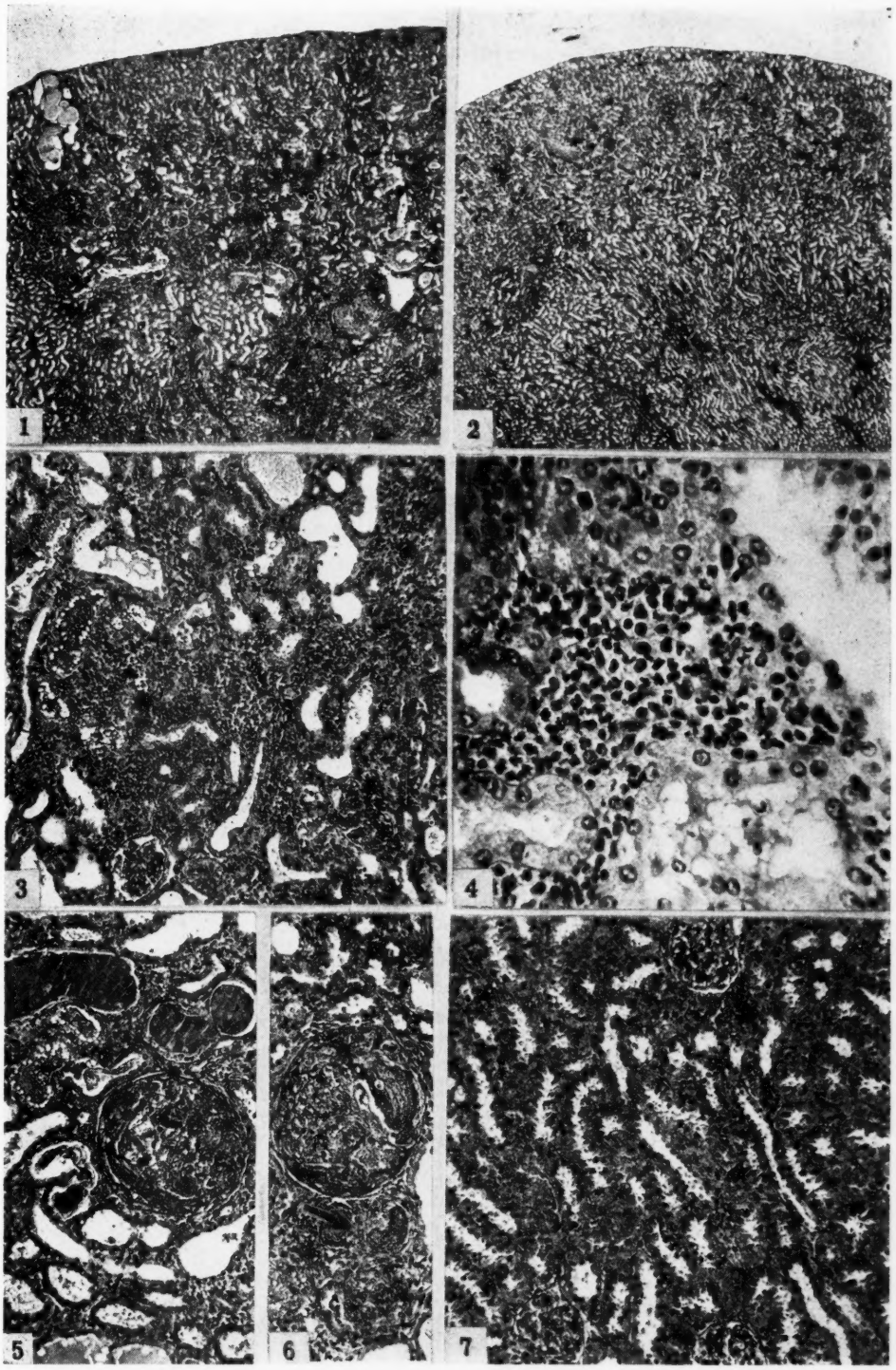

Plate VIII.—*(For legend see opposite page.)*

forced muscular exercise,[294] cold,[152] fever caused by ultrahigh-frequency radio emanations,[50] anoxia,[131, 146] treatment with various drugs,[152] x-rays,[362] transection of the spinal cord,[207] toxic tissue extracts,[441] and other damaging agents.[271]

There is still insufficient evidence to evaluate the changes in the ascorbic acid content of the adrenal during the general adaptation syndrome.[441]

The *thymus* also shows very conspicuous changes during the alarm reaction, inasmuch as it undergoes acute "accidental involution" which becomes most pronounced during the countershock phase when the adrenal cortex reaches its maximum development. This loss of thymus weight is preceded by histologic signs of nuclear pyknosis with consequent complete dissolution of the thymocytes. Large macrophages engulf the dead thymus cells and carry them away through the lymphatics. At the same time the thymic reticulum reverts to its original epithelial type, inasmuch as its cells become roundish or polygonal and rich in cytoplasm. They often form massive cell nests, resembling parathyroid tissue, new Hassal bodies or colloid-filled vesicles similar to those of the thyroid. When involution is most acute, the entire organ is distended with jellylike edema.[202, 361, 541-543, 545] During the acute stage, the thymic changes are identical with those seen in the so-called "caryoclastic crisis." It is noteworthy that an increase in the mitotic figures is but rarely seen in the thymocytes during the alarm reaction, while it appears to be fairly frequent after treatment with certain "caryoclastic drugs" such as arsenic.[293] It is possible, however, that this is merely the result of differences in dosage. As in the case of the adrenal response, the thymus and lymph node involution occasioned by exposure to damaging agents is now generally recognized as due to the alarm reaction mechanism and not to the specific effects of the agents used. This has been demonstrated in recent years for such stimuli as transection of the spinal cord,[207] cold,[496] and anoxia.[146]

The *lymph nodes,* the *spleen,* and *other lymphatic organs* are almost as markedly affected as the thymus, although they do not involute quite as rapidly

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Plate IX.—Hormonally produced renal and cardiac lesions similar to those occurring in diseases of adaptation. *Fig. 1.* Normal kidney. Cross section through normal kidney of a female dog (final body weight 19 pounds) which acted as a control for *Figs. 3* and *4*. *Fig. 2.* Normal kidney. Surface view of kidney shown in *Fig. 1*. *Fig. 3.* Experimental nephrosclerosis. Cross section through kidney of a female dog (final body weight 19 pounds) treated with anterior lobe extract, desoxycorticosterone acetate and thyroxin for ten weeks. As explained in the text, thyroxin augments the nephrotoxic action of both anterior lobe and corticoid preparations. Note great increase in renal size, mainly due to cortical enlargement. The organ is reminiscent of the "large white kidney" of human pathology. *Fig. 4.* Experimental nephrosclerosis. Surface of the kidney shown in *Fig. 3*. Note "flea bitten" appearance due to numerous glomerular hemorrhages. These were histologically confirmed and microscopic examination also showed signs of typical nephrosclerosis. *Fig. 5.* Experimental fibrinous pericarditis produced with desoxycorticosterone acetate and sodium chloride treatment in the dog by giving daily subcutaneous injections of 20 mg. of desoxycorticosterone acetate for seven weeks and then 2 per cent sodium chloride solution to drink ad lib. The animal died within forty-eight hours of the sodium chloride administration, with an enormous amount (36 c.c.) of pericardial transudate containing excessive quantities of potassium, sodium, chlorine, and fibrin. *Fig. 6.* Myocarditic (Aschoff?) nodule produced by desoxycorticosterone overdosage in the rat. Note granuloma tissue between otherwise normal myocardial fibers. *Fig. 7.* Myocarditic (Aschoff?) nodule. High magnification of a nodule similar to that shown in *Fig. 6*. Note several slightly basophilic, polymorphonuclear giant cells (Aschoff cells?) with characteristic fringy cell borders. *Fig. 8.* Myocarditic nodules (Aschoff?) in subendocardial layer of a papillary muscle produced in the rat by treatment with desoxycorticosterone acetate and sodium chloride. Note characteristic excentric location of the (partially hyalinized) blood vessel in this nodule. The center of the nodule consists of hyalinized material, in which several giant cells are detectable. (*Figs. 6, 7,* and *8* after Selye and Pentz: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**: 264, 1943.)

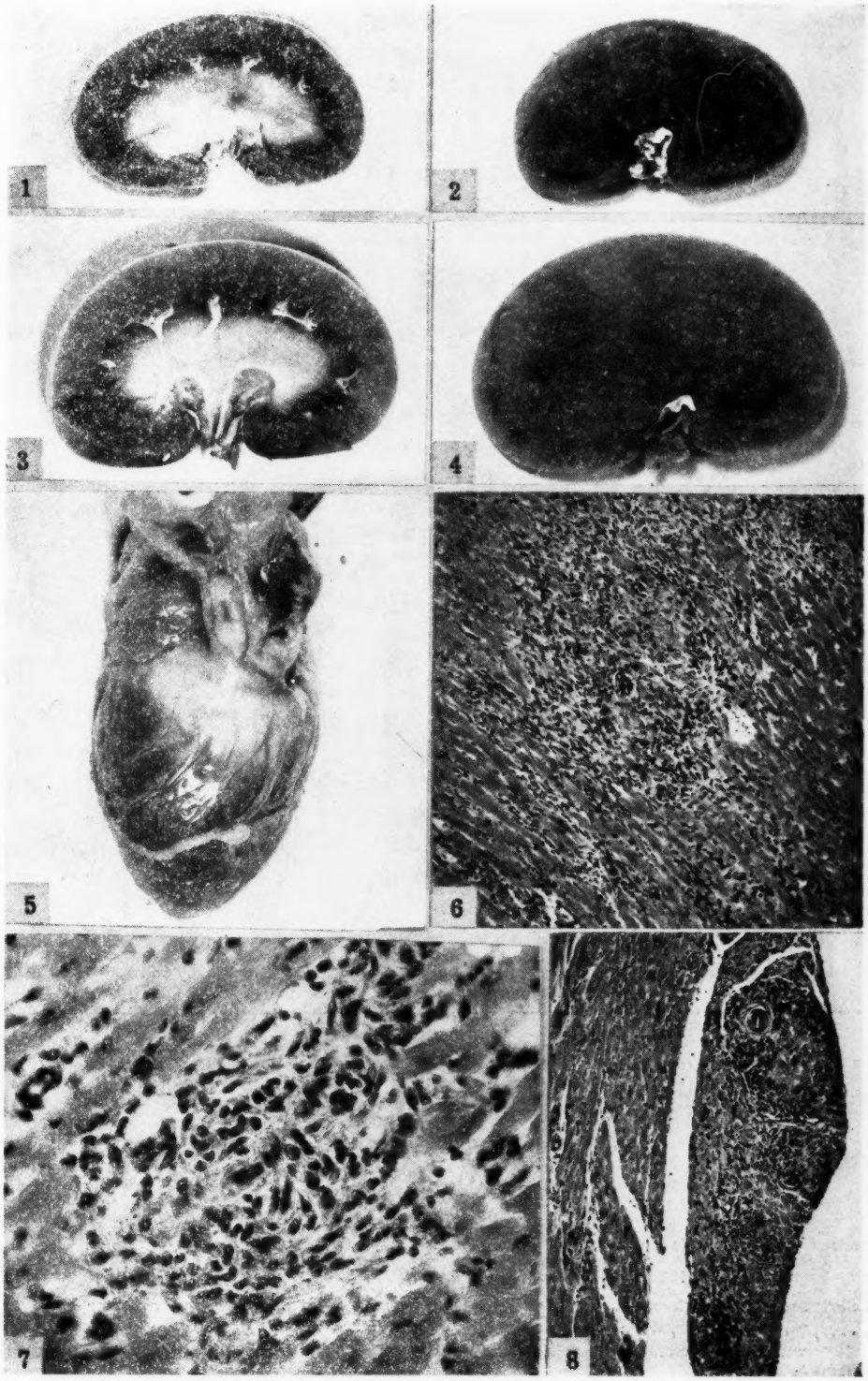

Plate IX.—*(For legend see opposite page.)*

nor is their involution as completely prevented by adrenalectomy.[202, 541-543, 545] Similar changes have been seen following burns in the lymph nodes and tonsils of man.[273] If the circulating blood volume is increased by intravenous infusions of saline, subsequent exposure to alarming stimuli may lead to the transformation of the ordinary lymph nodes into hemolymph nodes.[589]

The *pancreas* likewise undergoes acute involution during the alarm reaction. This affects mainly the acinar tissue whose cells discharge their zymogen granules, decrease in size, and may even become necrotic. Only in the immediate vicinity of the islets does the excretory parenchyma retain its normal appearance. As a result of this change, the organ, which is usually firm and of a white color, becomes very soft, translucent, and grayish or pink. In some cases, the individual Langerhans' islets with their surrounding "halos" of relatively normal parenchyma become readily visible to the naked eye. The islets themselves often show an increased number of nuclear pyknoses, but in some cases the impression is gained that active new formation of islet tissue occurs from the small ducts or that several islets unite into one "giant islet."[545] This acute involution cannot be regarded merely as the result of generalized tissue breakdown, intended to supply the organism with large amounts of nutritive material, since during the latter stages of the countershock phase the pancreas resumes its normal appearance even if no food is administered throughout the experiment. Such a temporary involution during the shock phase with subsequent restoration from endogenous sources is difficult to understand unless it is assumed that the pancreas contains especially readily available or valuable substances which are of particular use during an emergency.

Richardson and Young[500] noted that their "pancreatropic" pituitary extract causes changes in the Langerhans' islets which bear some resemblance to those seen during the alarm reaction, but they emphasized that these changes are not identical and probably quite unrelated. Similarly, Sergeyeva[606] observed discharge of zymogen granules from the acinus cells following vagus stimulation or choline administration. Here again, "halos" of unexhausted acinus cells remained in evidence only in the immediate vicinity of the islets. The author claimed that, in spite of the striking resemblance to the lesions char-

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Plate X.—Hormonally produced vascular lesions similar to those occurring during diseases of adaptation. *Fig. 1.* Periarteritis nodosa of the cardiac vessels produced with lyophilized anterior pituitary material in a rat receiving 1 per cent sodium chloride to drink. Note dark ring of subintimal hyalinization in one small artery (lower part of field) and inflammatory infiltration of the walls in the other (upper part of field). *Fig. 2.* Prevention of myocardial periarteritis nodosa by ammonium chloride. The animal whose cardiac muscle is shown in this picture received the same treatment as was given to the animal illustrated in *Fig. 1*, but in addition, 1 per cent ammonium chloride was added to the drinking water. Note complete absence of pathologic changes. *Fig. 3.* Experimental myocarditis produced by lyophilized anterior pituitary material in a rat receiving 1 per cent sodium chloride to drink. Note almost complete degeneration of myocardial fibers and their replacement by a fibrous granuloma tissue. The area probably corresponds to one of the many myocardial infarcts which develop under such experimental conditions, due to periarteritis nodosa of the cardiac vessels. *Fig. 4.* Prevention of experimental myocardial lesions by ammonium chloride. The rat whose myocardium is shown here received the same treatment as that illustrated in *Fig. 3* but in addition, 1 per cent ammonium chloride was added to the drinking water. Note complete absence of pathologic changes. *Fig. 5.* "Caterpillar cells" formed in a myocardial nodule of a rat treated with lyophilized anterior pituitary material and receiving 1 per cent sodium chloride to drink (indicated by arrows). *Fig. 6.* "Caterpillar Cells." Oil immersion view of an area of *Fig. 5*. Note two typical "caterpillar cells" with their nuclear chromatin arranged in the characteristic fashion (indicated by arrows).

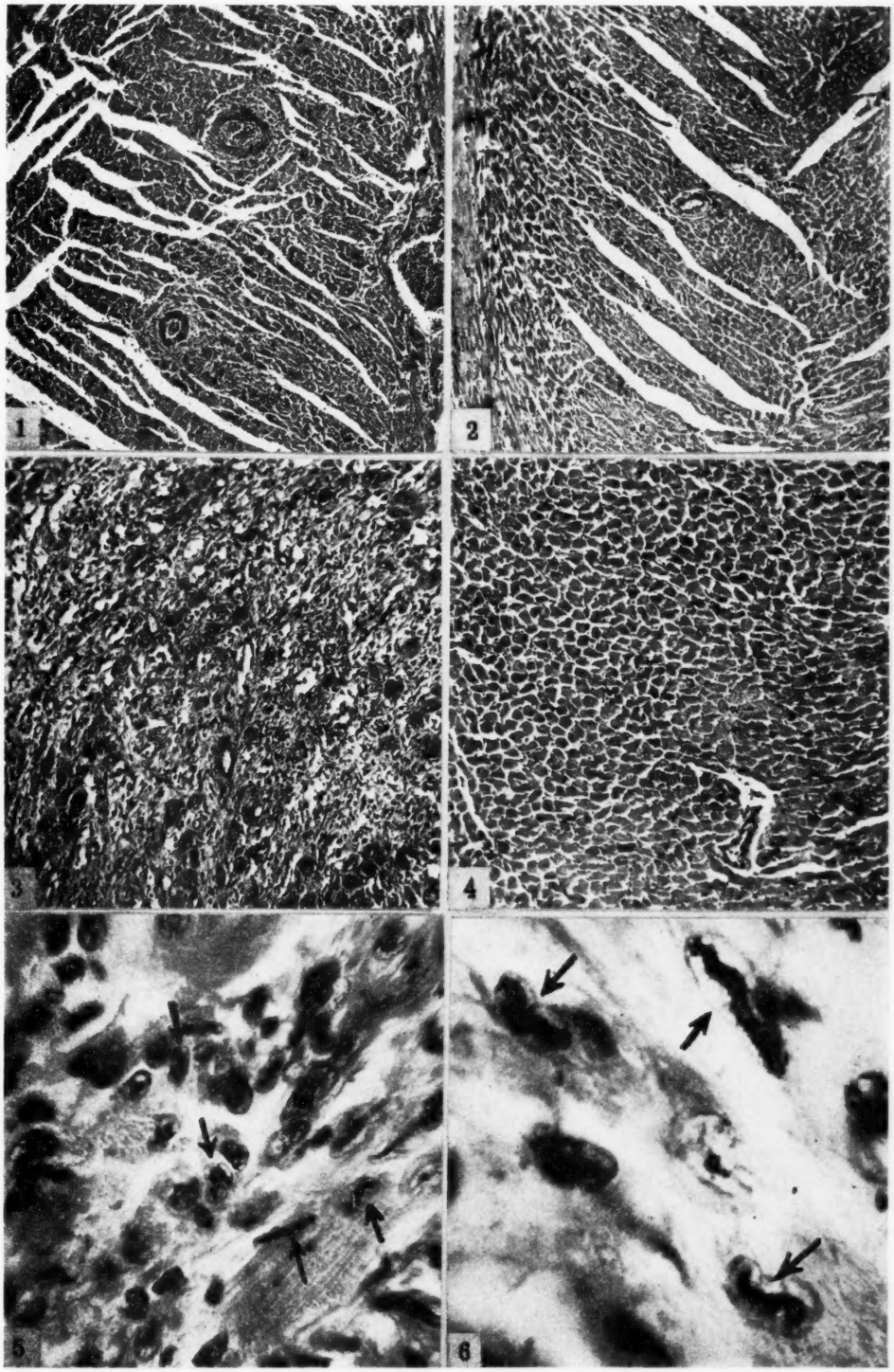

Plate X.—*(For legend see opposite page.)*

nor is their involution as completely prevented by adrenalectomy.[202, 541-543, 545] Similar changes have been seen following burns in the lymph nodes and tonsils of man.[273] If the circulating blood volume is increased by intravenous infusions of saline, subsequent exposure to alarming stimuli may lead to the transformation of the ordinary lymph nodes into hemolymph nodes.[589]

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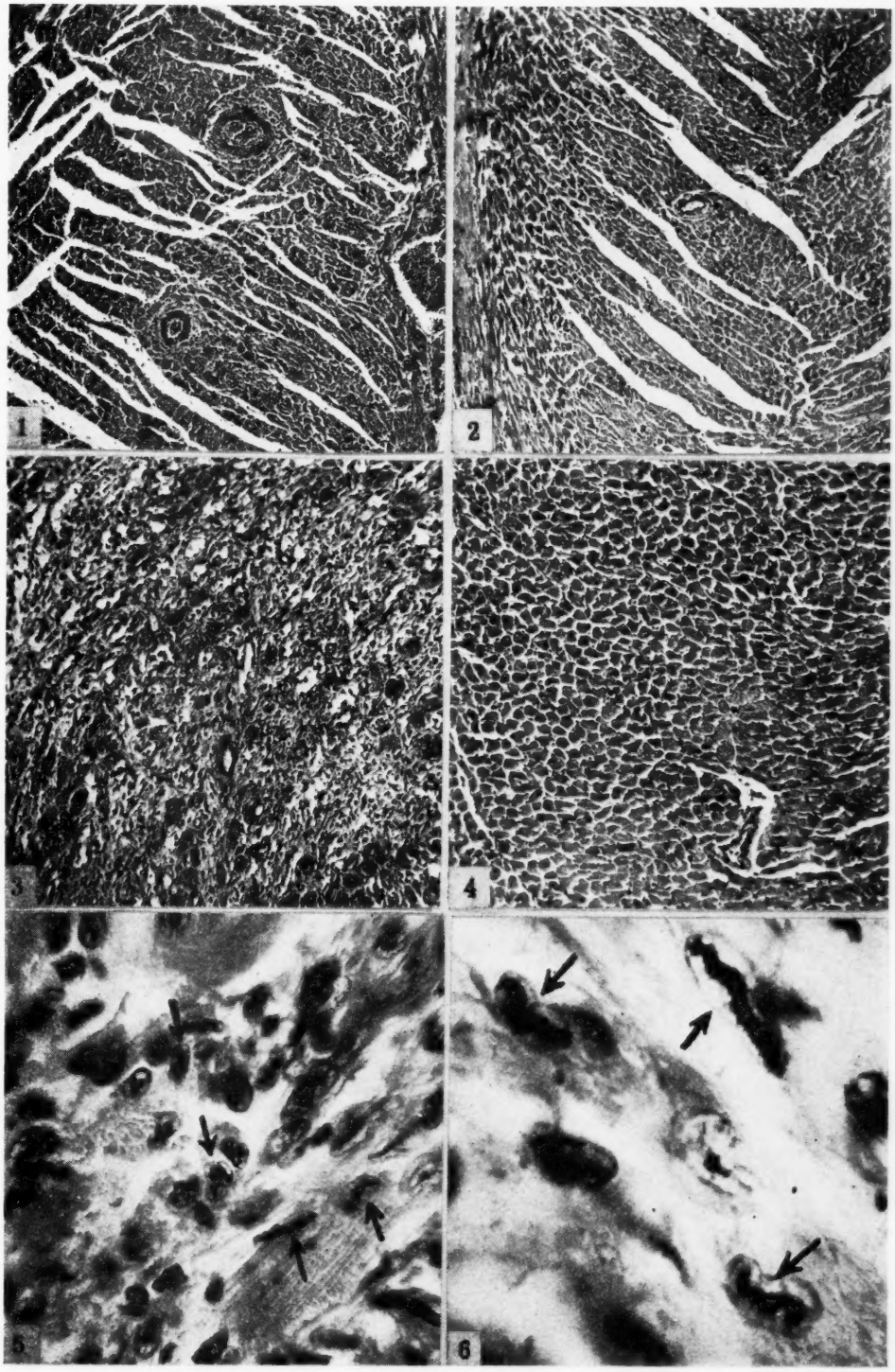

Plate X.—*(For legend see opposite page.)*

acteristic of the alarm reaction, these changes are specific. It would be difficult, however, to prove the specificity of this change in any particular instance, since a great many other drugs, such as atropine[26] and guanidine derivatives,[144] have been found to produce similar lesions. It is probable that the acute pancreatitis seen after burns[273] and certain cases of acute pancreatic necrosis have a similar etiology.

The anterior lobe of the *hypophysis* often shows degranulation, especially of the eosinophiles, and sometimes marked waves of nuclear pyknosis. The borderline between anterior and posterior lobe may become rather irregular, with signs of "basophilic invasion"[545] but these changes are inconstant. More recently it has been found that, in the rat, hypertrophy and hyperplasia of the anterior lobe basophiles are induced by such diverse agents as experimental nephritis, bilateral ligature of the ureters, injection of 10 per cent hydrochloride, ligature of the internal jugular veins, or injection of hypertonic fluids into the cerebral ventricles. It was concluded that "probably in all these instances, the pituitary changes are due to the same mechanism and constitute a form of the general adaptation syndrome to intensely damaging agents, as described by Selye."[269a] Further studies concerning histologic changes in the hypophysis during adaptation to stress would be most desirable since there is convincing physiologic evidence to show that this gland plays a very important role in the general adaptation syndrome (see section on "Theories Concerning the General Adaptation Syndrome").

The *thyroid* may display signs of atrophy and involution during the early stages and sometimes this is followed by a second phase of hyperplasia. Perhaps the latter has something to do with the thyroid-stimulating effect of various nonspecific substances, such as casein, tissue extracts, etc.[545] and the development of Graves' disease following sudden stress. Means[421] gave a table in his book on the thyroid in which he demonstrated the similarity between thyrotoxicosis and the alarm reaction, but these interrelations will have to be studied in more detail before they can be fully understood.

The *gonads* of both sexes undergo atrophy during the general adaptation syndrome. This has been interpreted as due to a "shift" in the hormone pro-

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Plate XI.—Hormonally produced vascular lesions similar to those occurring in diseases of adaptation. *Fig. 1.* Normal mesenteric vessels. Macroscopic view of a normal small intestinal loop of a rat. Note thin and regular mesenteric vessels. *Fig. 2.* Mesenteric periarteritis nodosa. Macroscopic view of a small intestinal loop of a rat chronically treated with desoxycorticosterone acetate. Note numerous beadlike, periarteritis nodosa nodules along the mesenteric vessels. *Fig. 3.* Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Low magnification of a section through mesenteric insertion on intestinal wall. Note thickening and infiltration of the transversely sectioned mesenteric arteries. *Fig. 4.* Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Transverse section through mesenteric artery, showing first stages of periarteritis nodosa. Medium magnification. Note deposition of a thin layer of hyaline material, underneath the somewhat irregular endothelial surface. The structure of the muscular coat is still well preserved but the adventitia shows some inflammatory infiltration. *Fig. 5.* Mesenteric periarteritis nodosa produced by desoxycorticosterone acetate overdosage in the rat. Somewhat more advanced stage of the same process as shown in *Fig. 4.* Note almost complete destruction of the endothelium with deposition of a fairly thick layer of hyalinized fibrinlike material on the vascular wall. The structure of the vessel is almost unrecognizable owing to heavy infiltration with leucocytes, many of which are eosinophilic. Some giant cells are also detectable. (Same magnification as *Fig. 4.*) *Fig. 6.* Mesenteric periarteritis nodosa produced by desoxycorticosterone acetate overdosage in the rat. Transverse section through mesenteric artery, showing final stages of periarteritis nodosa. Note thick layer of hyalinized fibrin, lining the vascular lumen. The vessel walls have undergone partial necrosis and hence appear somewhat homogeneous. (Same magnification as *Figs. 4* and *5.*)

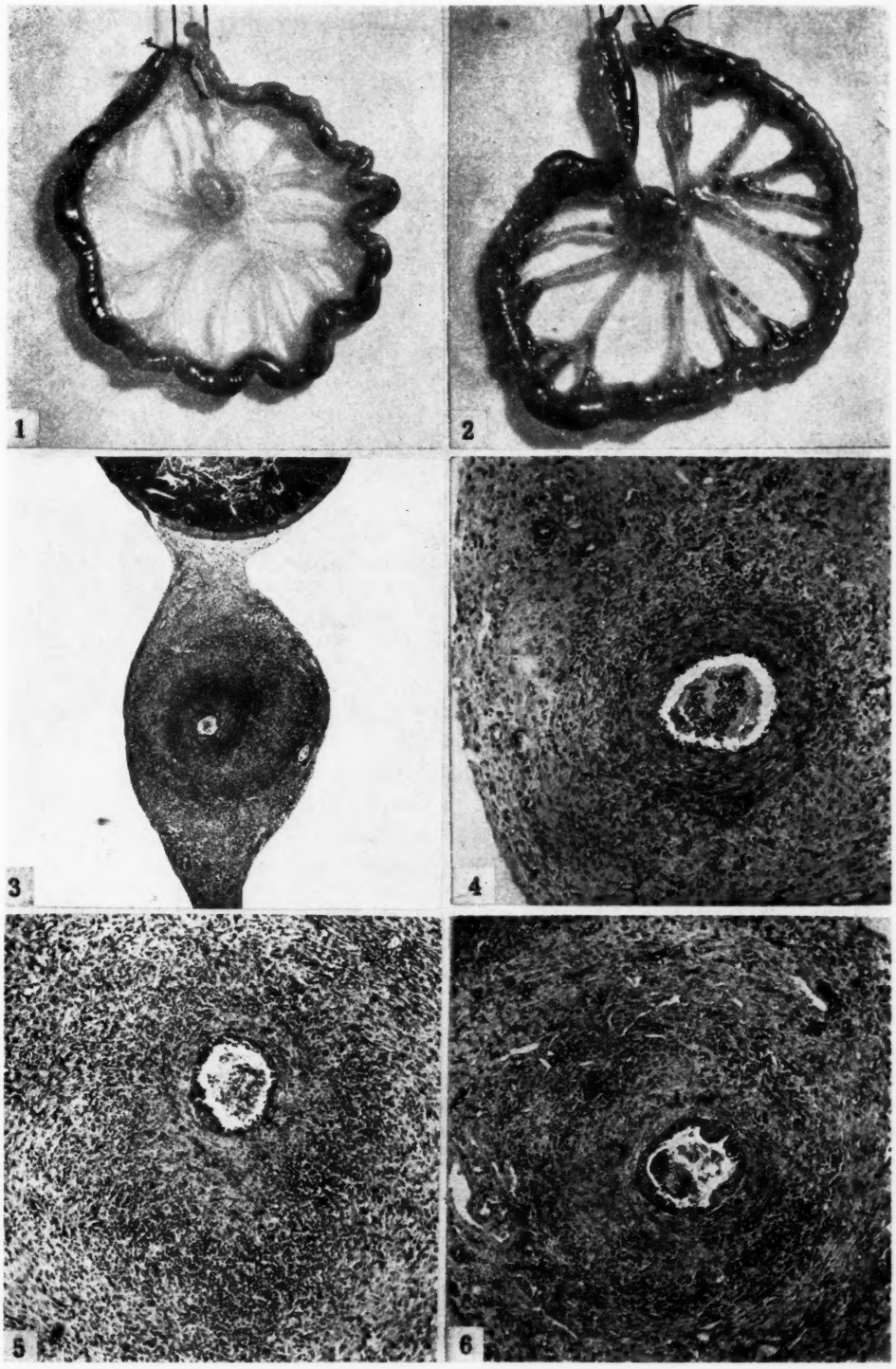

Plate XI.—*(For legend see opposite page.)*

duction of the pituitary which in times of emergency produces more of such vitally necessary hormones as the adrenotropic principle at the expense of its gonadotropic hormone output.[58a, 146, 200, 350, 547, 565]

The *blood count* shows very characteristic changes during the alarm reaction. There is a pronounced increase in the total white cell count due to neutrophilic leucocytosis with relative lymphopenia. These changes are particularly obvious in the countershock phase and may be preceded by leucopenia during the shock phase, especially if the damage is severe. Animals in which the leucopenia persists for an unduly long period are usually irresistant and succumb without showing any signs of countershock.[130, 133, 254] This nonspecific leucocytosis may be preceded by a decrease and followed by an increase in eosinophiles.[132, 133] Boyd and his associates[72] claimed that, in rabbits in which an alarm reaction was produced by hemorrhage, no leucocytosis developed and concluded that this change is not characteristic of the alarm reaction. The table given in their paper, however, indicates an increase in the total leucocyte count from the normal of 8,450 to 12,000 in twenty-four hours.

In the light of these observations, the leucocytosis observed by previous investigators following muscular exercise,[28, 170, 178, 239, 533] treatment with various drugs,[23, 65, 85, 471] tissue extracts,[464, 526] bacterial toxins,[464] exposure to cold,[175, 303, 519] operative procedures,[347, 532] infections,[145, 186-188, 279] anaphylaxis,[58, 666, 672, 683] burns,[273, 348] ultraviolet rays,[660] and x-rays[493] can hardly be regarded as the specific effect of these agents and is much more probably due to the alarm reaction produced by them. It is interesting that many of the afore-mentioned authors emphasized that in cases of severe damage, leucopenia may precede or replace the leucocytosis. Recently Dougherty and his associates[155] brought fourth important evidence showing that the lymphopenia elicited by alarming stimuli is produced through the same pituitary-adrenal cortex mechanism which is responsible for the thymus and lymphatic tissue involution during the alarm reaction. Perhaps some of the leucopenias produced by infections and intoxications[625b] may be explained also on this basis.

The red cell count and the hematocrit values show a marked increase during the alarm reaction, especially during the shock phase. This may be preceded

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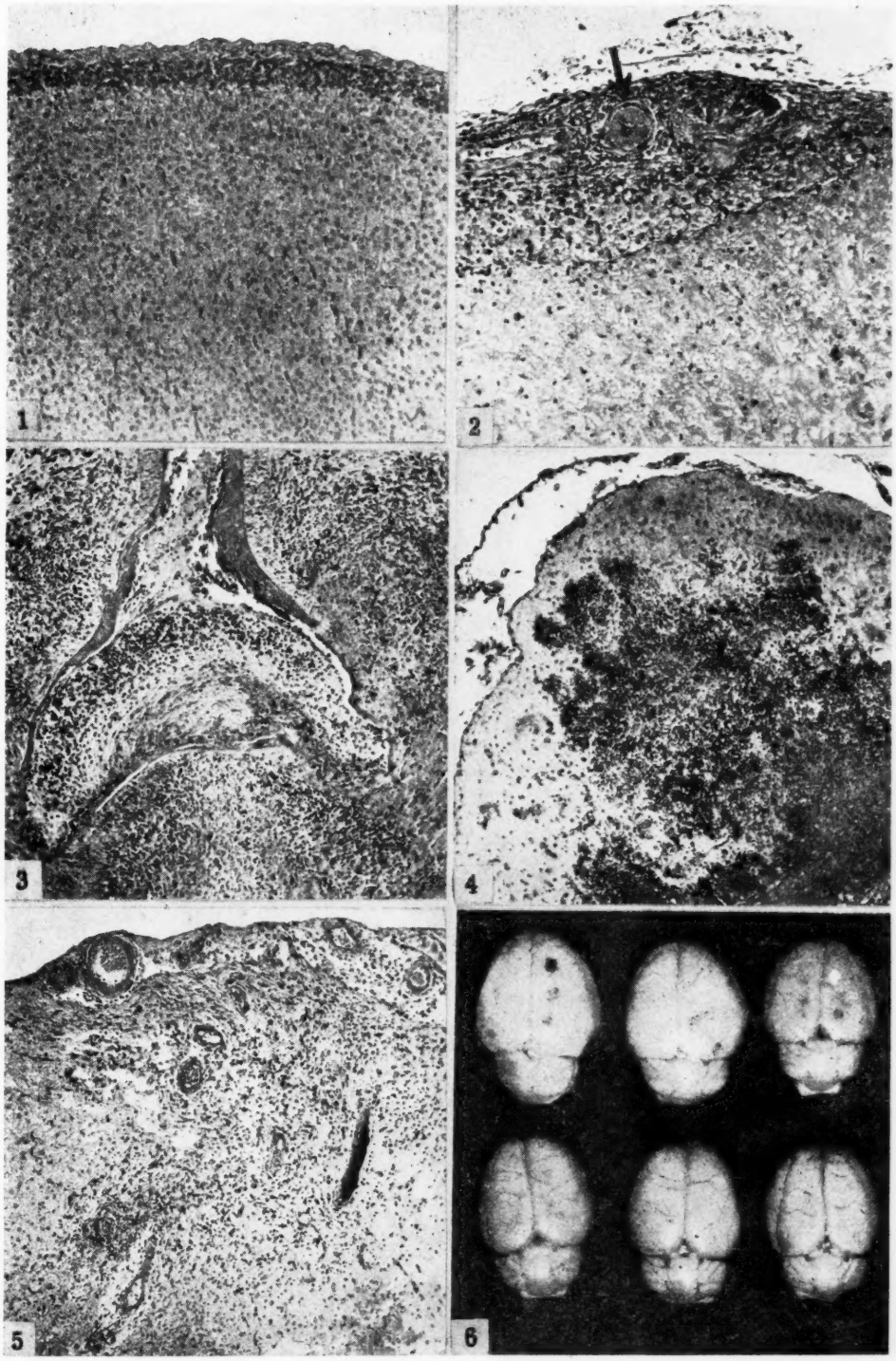
Plate XII.—Hormonally produced vascular lesions similar to those occurring in diseases of adaptation. *Fig. 1.* Normal adrenal. Suprarenal cortex of a rat (control for *Fig. 2*). *Fig. 2.* Periarteritis nodosa of the adrenal vessels produced by chronic overdosage with an alkaline anterior lobe extract and administration of 1 per cent sodium chloride instead of drinking water. Note the subintimal hyalinization of the arteriole in the capsule (arrow) and the inflammatory infiltration around it. The adrenal cortex is almost completely necrotic, due to interference with its blood supply. Only a thin layer of subcapsular cells remain. It will be recalled that, unlike desoxycorticosterone acetate, anterior lobe extracts do not tend to produce widespread periarteritis nodosa but usually affect only the vessels of the heart and adrenal cortex. *Fig. 3.* Thrombus formed at the bifurcation of a mesenteric artery following desoxycorticosterone acetate overdosage in the rat. Note thick layer of fibrin which lines the vessel wall and a U-shaped thrombus which almost completely occludes the lumen. The thrombus consists mainly of fibrin, platelets, and leucocytes (this, as well as *Figs. 1, 2, 3, 4, 5* and *6* of Plate IX, after Selye and Pentz: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions. Canad. M. A. J. **49**: 264, 1943.) *Fig. 4.* Brain hemorrhages, secondary to periarteritis nodosa, following desoxycorticosterone acetate overdosage in the rat. Note extensive hemorrhage underneath the cerebral cortex. *Fig. 5.* Periarteritis nodosa of the brain vessels produced by chronic desoxycorticosterone acetate overdosage in the rat. Section through the brain, showing hyalinization of some arterioles on the surface of the cerebral hemisphere. Note also tissue edema and perivascular round-cell infiltration. *Fig. 6.* Brain hemorrhages produced by periarteritis nodosa of the cerebral vessels, following desoxycorticosterone acetate overdosage in the rat. Macroscopic view of three brains with hemorrhagic patches, due to periarteritis nodosa of the surface vessels (top row) and three normal brains of untreated control rats (bottom row). Note the rather characteristic arrangement of the hemorrhages along a sagittal, paramedian line.



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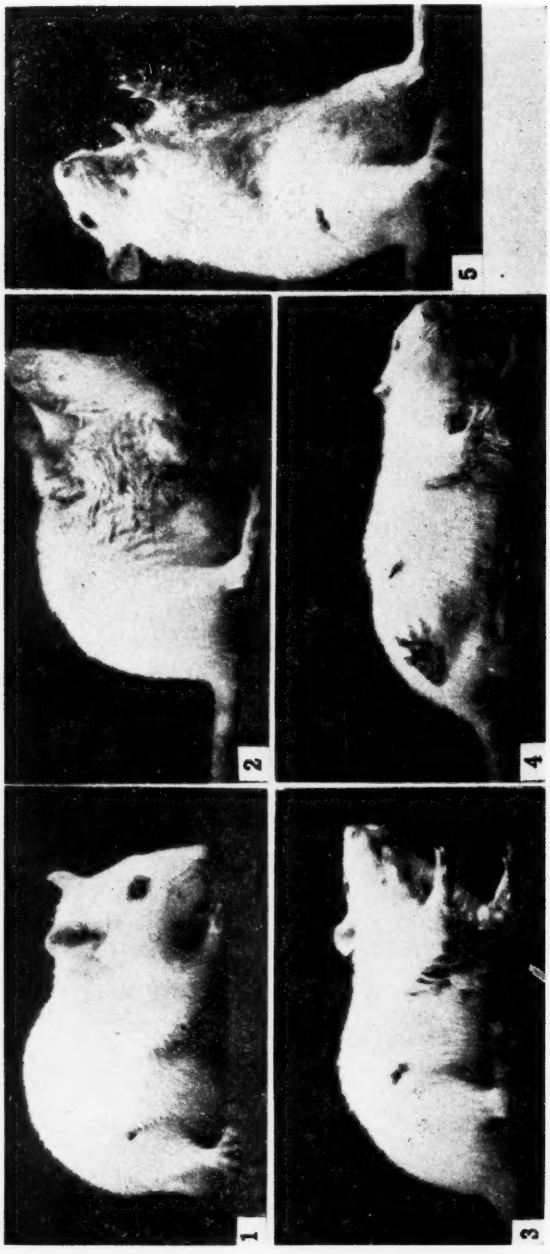

Plate XIII.—Motor disturbances due to periarteritis nodosa of the brain. *Fig. 1.* Desoxycorticosterone acetate treated rat with periarteritis nodosa of the brain, shown during rests between two spells. *Figs. 2* and *3.* Same rat shown during successive stages of a typical clonic spell with rotation of the shoulder girdle and head towards the left. *Fig. 4.* Final stage of the same attack, with animal rolling over completely to the left. *Fig. 5.* Another similarly treated rat in which the nature of the clonus is such that the entire front part of the body is thrown back during each attack. These spells are characteristic of cerebral hemorrhages due to experimental periarteritis nodosa of the brain. (*Figs. 4, 5,* and 6 of Plate XII and all Figs. of this plate, after Seyle, Beland, and Sylvester: Brain Lesions Following Prolonged Overdosage With Desoxycorticosterone Acetate, Exper. Med. & Surg. 2: 224, 1944.)

Plate XIV.—Hormonal production of arthritis. *Fig. 1.* Normal metatarsal joint of a rat. Control for subsequent figures. *Fig. 2.* Acute arthritis produced by desoxycorticosterone acetate overdosage in the rat. Note edematous, synovial membrane and exudate in metatarsal joint cavity. *Fig. 3.* Necritizing arthritis and periarthritis produced by desoxycorticosterone acetate overdosage in the rat. Note hyaline necrosis of the synovial membrane and cellular infiltration of the connective tissue around the joint. The joint surface itself is normal. *Fig. 4.* Arthritis produced by treatment with alkaline anterior pituitary extract. Note edema and round-cell infiltration of the synovial membrane with some necrotic material projecting into the metatarsal joint cavity. *Fig. 5.* Newly formed periarterial bone in the metatarsal region of a rat treated with alkaline anterior pituitary extract.

Plate XIV.—*(For legend see opposite page.)*

by a transient decrease[132, 133, 312] and is frequently accompanied by reticulocytosis.[130, 133] Among all the alarming stimuli so far studied, only muscular exercise caused an almost immediate and persistent decrease in the red cell count, which was but rarely preceded by a transitory rise during the peak of the shock phase.[133, 312, 563] This blood dilution must be regarded as a specific effect of exercise, but even this stimulus leads to the usual typical nonspecific leucocytosis.[133] The blood-diluting effect of strenuous exercise has been seen also in man.[426]

Gastrointestinal ulcers are likewise characteristic of the shock phase. They are most frequently seen in the stomach and small intestine and are usually accompanied by more or less massive hemorrhages into the intestinal lumen.[541, 543, 545] They are evidently signs of damage and occur even more readily than usual in adrenalectomized animals which are unable to develop well-marked countershock phenomena. These ulcers are probably comparable to the acute gastrointestinal erosions which are so frequently observed during shock in man where they account for the dark coffee-colored vomitus seen under such conditions. They often develop following burns (''Curling's ulcer''),[273] intense emotional excitement (e.g., ''air-raid ulcers''),[575] et cetera. An excellent description of emotional changes in the human gastric mucosa (including the formation of erosions) was made on a patient with a gastric fistula.[692] In animals, similar changes occur after exposure to intense solar radiation,[480] low oxygen tension,[231] x-rays,[362] spinal cord transection,[207, 545, 597] head injuries,[633] or any other intense alarming stimulus. The healing of the gastric ulcers is very rapid and usually far advanced twenty-four hours following exposure to damaging agents.[128] This change is always accompanied by other symptoms of the alarm reaction.

In cases of particularly acute and severe damage, that part of the cecum which in the rat corresponds to the human appendix may be specifically affected and show marked hemorrhagic edema similar to that observed during the first stages of acute appendicitis. It has been concluded that perhaps certain cases of acute appendicitis in man may be due also to similar systemic rather than local causes. Since some investigators believe that the liberation of a histamine-like metabolite from the tissues may be the basic cause of shock symptoms, it is of particular interest that intravenous administration of histamine proved especially effective in eliciting such acute appendicular lesions.[544, 546]

Hyperemia of the *lungs,* often accompanied by edema and even acute pneumonia, may also occur during the alarm reaction, but these changes are not constant. At the same time, pleural transudates are often observed which are especially pronounced if the alarm reaction is produced by peritoneal interventions.[541, 543] It appears probable that the pneumonia observed following x-rays,[173] intense solar radiation,[480] burns, intestinal obstruction, surgical trauma,[435] toxic doses of various drugs,[435, 561] etc., are also merely signs of the alarm reaction rather than specific changes. It is not clear, however, whether or not the acute lung edema produced by anoxia is a manifestation of the alarm

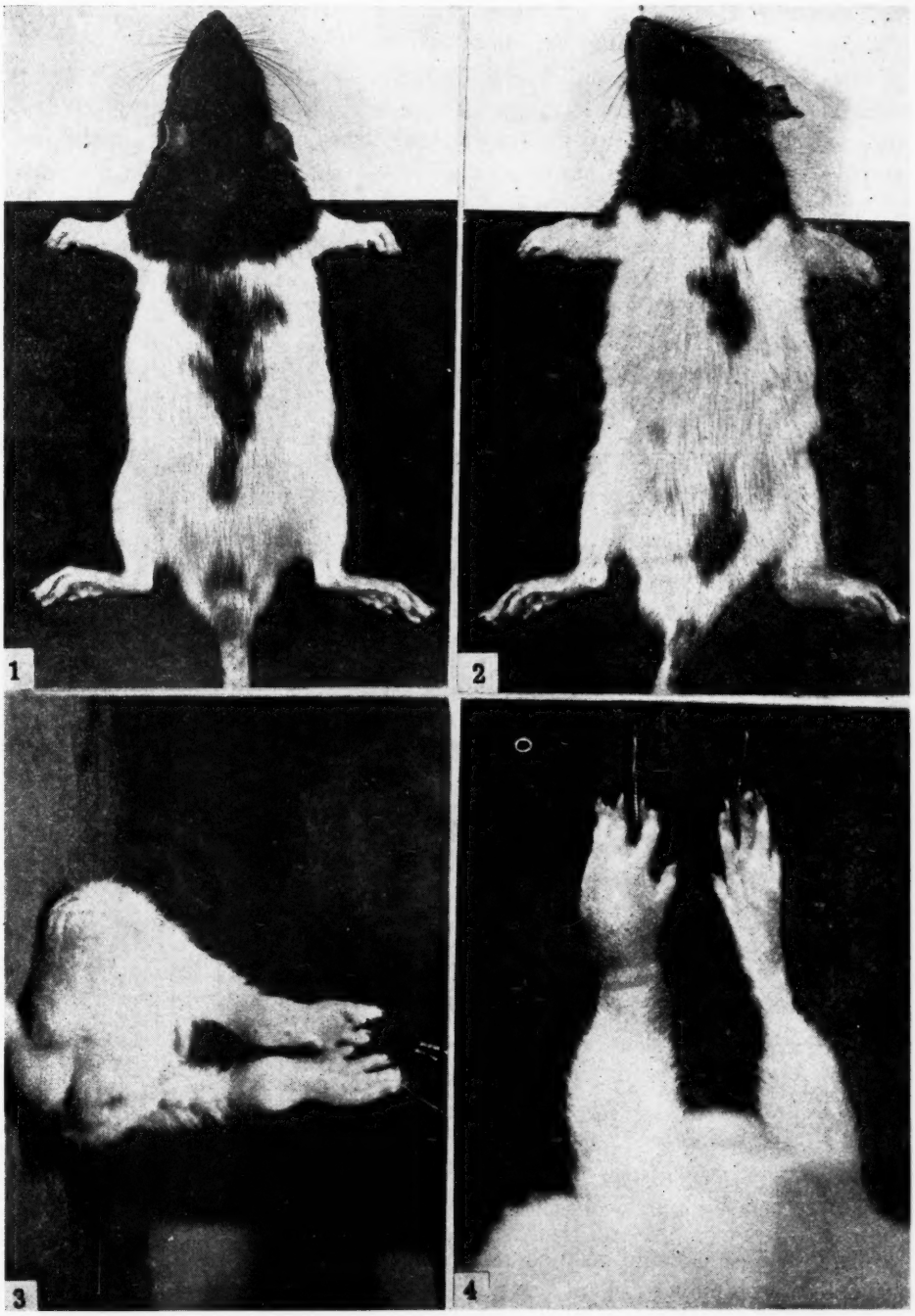

Plate XV.—Hormonal production of arthritis. *Fig. 1.* Normal rat, control for *Fig. 2*. *Fig. 2.* Inflammation of metatarsal joints in two front paws and right hind paw of a rat chronically treated with anterior pituitary extract. *Fig. 3.* Arthritis in both hind paws of a rat chronically treated with anterior pituitary extract. *Fig. 4.* Acute arthritis in the tarsal and metatarsal joints of the left hind paw in a rat chronically treated with anterior pituitary extract. Compare with the corresponding right hind foot, which, in this case, was not affected.

reaction; although, like most manifestations of the latter, it is more severe and more frequent in fasting than in fed animals.[357, 359]

The *liver* often shows only signs of cloudy swelling and a decrease in size, which may partly be accounted for by the decrease in blood volume.[545] It may, however, show more extensive atrophy and degenerative changes with focal necroses, sometimes accompanied by intense fatty infiltration,[203, 567] which Leblond et al.[362, 363] consider to be typical of the alarm reaction.

Nomenclature and Symptomatology of the General Adaptation Syndrome (Schematized).

Explanation of Symbols: ↑ = Increased, ↓ = Decreased } magnitude of change indicated by size of arrow.
↕ = Normal unchanged.
* = The changes in these organs are dependent upon a high Na intake
? = No conclusive data published on this subject.

Plate XVI.—Nomenclature and symptomatology of the general adaptation syndrome. Schematic representation of the most prominent morphologic and metabolic changes during the general adaptation syndrome and the diseases of adaptation.

The *kidneys* show no very obvious changes during the alarm reaction. Occasionally there may be cloudy swelling and some albuminuria, or even hemoglobinuria, but this is by no means constant.[545] Conversely, during the stage of resistance and the stage of exhaustion of the general adaptation syndrome, nephrosclerosis or even acute nephritis occurs, especially in animals sensitized by unilateral nephrectomy and a high sodium intake. These renal changes are

accompanied by a malignant type of hypertension, proteinuria, and sometimes widespread periarteritis nodosa with cardiac nodules which resemble the Aschoff bodies of rheumatic fever. Apparently not all alarming stimuli are equally capable of eliciting this syndrome; exposure to cold is most effective in this respect.[574] These lesions are essentially identical with those produced by overdosage with crude anterior lobe extracts or desoxycorticosterone acetate, hence it was thought that a deranged hormonal adaptive mechanism to strain may be the cause of the corresponding maladies in man. (See also section on "Clinical Implications of the General Adaptation Syndrome," especially for discussion of cardiovascular changes.)

The crystalline lens of the *eye* shows pronounced cloudiness in cases of sublethal shock during the first phase of the alarm reaction but, if the animal recovers, the lens clears up again.[545] The fact that these changes in the lens are truly nonspecific is further corroborated by the observation that, in animals, they may be elicited by exposure to cold,[545] anoxia,[44] various types of narcotics,[32] and adrenalin overdosage.[627, 628] During the dehydration of diabetic coma they occur also in man.[356]

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(To be concluded.)

American Academy of Allergy

NEWS AND NOTES

THE ALLERGY UNIT AT THE UNIVERSITY OF ILLINOIS COLLEGES OF MEDICINE AND PHARMACY

The University of Illinois has organized a unit for the purpose of training physicians in allergy. The Departments of Biological Chemistry, Bacteriology, Dermatology, Medicine, Pediatrics, Pharmacology, Ophthalmology, Otolaryngology, Psychiatry, in the College of Medicine, and the Departments of Botany and Pharmacognosy, in the College of Pharmacy, are cooperating. This is the first attempt to present a comprehensive integrated training covering both the fundamental and the clinical aspects of the subject. The minimum course is of twelve months' duration on a full daily schedule. Particular emphasis is placed on the fundamental sciences and internal medicine. Students who wish to do advanced work in fundamental science and carry on research may register in the Graduate School and work toward a master's degree after the satisfactory completion of the first year's work. The first year began Jan. 7, 1946, with registration of ten students and two research fellows.

The following is an outline of the work of the first year:

1. *Immunochemistry.*—12 weeks, 2 hours per week. The fundamental aspects of the chemistry of antigens and antibodies and the nature of their action.

2. *Immunology.*—12 weeks, 2 hours per week. The basic facts in the broad field of immune reactions, considering primarily the various serologic phenomena and their means of production and identification.

3. *Physiology.*—12 weeks, 2 hours per week. A review of physiology and the various symptoms which are primarily responsible for allergic manifestations.

4. *Pharmacology.*—12 weeks, 1 hour per week. The role of histamine and trypsin and related substances in the production of allergic manifestations and the consideration of the means by which the drugs used therapeutically act.

5. *Botany.*—12 weeks, 5 hours per week. Plant anatomy, toxonomy, morphology of pollen grains, and pollen counts. Field trips will be taken in order to learn to recognize the common plant excitants of allergic syndromes.

6. *Preparation of Allergens.*—12 weeks, 4 hours per week, 1 hour lecture, 3 hours laboratory. Chemistry of proteins and their methods of extraction. Also the methods of preparing oleoresins. Students will prepare various extracts.

7. *Clinical Allergy.*—36 weeks, 1 hour per week. An introduction to fundamental principles and a detailed consideration of etiology, diagnosis, and therapy of the common allergic syndromes with emphasis on the respiratory system. This course will be given in conjunction with attendance at the allergy clinics which will be 8 hours per week, through the year.

8. *Pediatric Allergy.*—24 weeks, 2 hours per week. The growth of the development of the normal child, deviation of the allergic child, and manifestations of allergy in various systems. This course will be given in conjunction with work in the pediatric clinic.

9. *Dermatology.*—12 weeks, 1 hour per week. Dermatoses which arise on the basis of sensitization mechanisms. Their differential diagnosis, as well as a consideration of the skin as an immunologic organ. This course will also be given with work in dermatology clinics which will be 3 hours per week for 24 weeks.

10. *Internal Medicine.*—Internal medicine will be considered throughout the entire year by having the student attend medical ward rounds and medical seminars, but in addition lectures will be given on internal medical syndromes in which sensitization mechanisms apparently play a prominent role. Lectures will also be given on the interrelationships of asthma with the circulatory and respiratory systems. On the average 6 hours per week throughout the year will be devoted to medicine.

11. *Psychosomatic Medicine.*—The principles of psychosomatic medicine and the psychodynamics of asthma with case demonstrations, which will take about 2 hours per week for 6 months.

12. *Miscellaneous.*—Courses and where indicated clinic work will be given in otolaryngology, anesthesiology, radiology, and dietetics.

During the second and third years the student will elect work in one or more of the following subjects: immunochemistry, immunology, serology, botany, and mycology. The emphasis will not be on the formal didactic instructions but rather on clinical training and opportunities for research.

A REPORT OF THE CLINICAL STUDIES ON THE USE OF PYRIBENZAMINE IN ALLERGIC DISEASES BY THE COMMITTEE ON PHARMACEUTICALS AND MEDICAMENTS OF THE AMERICAN ACADEMY OF ALLERGY

During the past few years various chemical compounds having a pharmacologic effect antagonistic to histamine have been developed. The Ciba Company has produced a drug called Pyribenzamine, which has been carefully studied by the Company from the standpoint of its pharmacologic and toxicologic effect. This experimental use of the drug indicated its applicability to certain types of allergic disease in man. In keeping with its customary caution, Dr. Yonkman of the Ciba Company, approached the Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy and offered to supply this drug for trial before any attempt was made to place the drug on the market for general use. The following report represents the consolidated result of those physicians to whom the drug was supplied for evaluation. These were as follows: Doctors Albert,

TABLE I

CONDITION	NUMBER OF CASES	IMPROVED	UNIMPROVED BENEFITED	(PER CENT)
Vasomotor rhinitis (nonseasonal)	277	164	113	59
Vasomotor rhinitis (seasonal)	104	56	48	54
Asthma (nonseasonal)	211	65	146	31
Asthma (seasonal)	11	5	6	45
Urticaria (acute)	121	94	27	77
Urticaria (chronic)	97	76	21	78
Dermagraphism	23	18	5	78
Pruritis	21	12	9	57
Eczema	9	2	7	22
Histaminic headache	5	3	2	60
Dermatitis (atopic)	59	30	29	51
Eczematous dermatitis	5	1	4	20
Dermatitis (unclassified)	7	4	3	57
Ménière's disease	5	1	4	20
Gastrointestinal allergy	7	2	5	28
Ulcerative colitis	1		1	0
Cold allergy	5	2	3	40
Visual disturbances	3	1	2	33
Drug rash	1		1	0
Migraine	6	1	5	17
Total	978	537	441	

Baer, Blanton, Blumstein, Bullen, Chobot, Cooke, Davison, Dundy, Feinberg, Glaser, Green, Grolnick, Harkavy, Jeffry, Metzger, Prickman, William Sherman, Squier, Sulzberger, Swineford, and Zohn. This report includes a total of 978 cases. (See Table I.)

It seems obvious from this record that Pyribenzamine is a useful palliative drug in certain allergic diseases, namely, acute vasomotor rhinitis, seasonal and nonseasonal, and acute urticaria. It appears to be less effective in the relief of asthma and dermatitis. In other words, it is most effective in those cases of the immediate wheal reaction. Certain side effects were noted in 168 cases. (See Table II.)

TABLE II. SIDE EFFECTS OF PYRIBENZAMINE

Sleepiness	61
Nausea	26
Urticaria	1
Dizziness	17
Blushing of skin	1
Vomiting	5
Early menses	1
Headache	12
Dry mouth	6
Nervousness	7
Tachycardia	4
Heartburn	1
Paresthesia	1
Wakefulness excitement	7
Gastrointestinal cramps	8
Ocular accommodation difficulties	3
Weakness	1
Typical symptoms of diabetes insipidus	1
Chills	2
Dysuria	3
Total	168

It will take a longer time to make a final evaluation of this drug, but it seems safe to say that at present it is very useful for symptomatic control. The question of tolerance remains to be determined, but there is some indication that tolerance might be established if used over a long period of time. Pyribenzamine is not a cure for allergic diseases, for in cases studied it was necessary to continue the drug unless the cause was found and removed. The Committee feels that it is justified in advising that the drug be released to the medical profession for proper use as an adjuvant in the management of allergic diseases.

The Committee wishes to express its appreciation for the cooperation of the Ciba Company in the preliminary evaluation of this drug.

ROBERT CHOBOT, M.D., Chairman.

June 26, 1946

Mr. J. Harvey Black, Executive Secretary
American Association for the Study of Allergy
1405 Medical Arts Building
Dallas, Texas

Dear Mr. Black:

The National Society for Medical Research was founded in 1946 under the sponsorship of the Association of American Medical Colleges.

The objective of the Society is to advance and encourage research and teaching in Biology, Medicine, Dentistry, Pharmacy, and Veterinary Medicine, by informing the public regarding the necessity, the humane character, and the accomplishments of animal experimentation.

Such a Society has become necessary for several reasons. *First*, the Hearst Press has adopted Antivivisection as a national editorial policy. *Second*, within one year Antivivisec-

tion legislation has had to be defeated in the District of Columbia, Maryland, Pennsylvania, New York State, Massachusetts, and Illinois; other campaigns are on the immediate horizon. *Third*, there are in our country at least 100 Antivivisection Societies, though some have a different name, which are constantly, in various ways, hampering animal experimentation. *Fourth*, when a new discovery in the Zoological and Medical Sciences is announced and publicized, it is exceedingly rare that the source of the discovery, namely animal experimentation, is acknowledged. *Fifth*, since ignorance is fertile soil for false, harmful, and malicious propaganda, otherwise intelligent laymen, and even physicians and nurses, are aroused by the malignant antimedical and antiscientific propaganda of Antivivisectionists. *Sixth*, during the past twenty-five years, many scientists have had to direct much time and energy toward opposing Antivivisection legislation and such legislation is more threatening today than yesterday: *Seventh*, education is a duty of those who know.

The Society proposes to conduct a scientific educational program for a minimum period of five years. It has recently engaged a staff of experienced personnel in the field of public relations and ancillary activities. The educational program will be conducted on a national scale at various levels.

The success of the Society requires the moral support of every organization and institution which is directly or indirectly based on animal experimentation.

The Society will have two types of members, contributing and non-contributing.

We invite the organization of which you are an officer to become a Non-contributing Member. In order to accelerate the growth of the present body of moral support behind the Society, we should like for you to act as soon as possible on this matter. The name of your organization or institution will be printed on the back of the letterheads of the Society.

We also require financial support. Medical Schools have to date contributed $9,000.00 to the Society. This will cover only one-third of the anticipated annual budget. Any amount which your organization or institution may be able to contribute will be gratefully accepted.

Yours very truly,

A. J. CARLSON, President.
A. C. IVY, Secretary-Treasurer.

P.S.: The Society has been incorporated in the State of Illinois as a non-profit institution.

July 16, 1946

The National Society for Medical Research
252 East Washington Street
Chicago 2, Illinois
Attention: Dr. A. C. Ivy, Secretary-Treasurer

Gentlemen:

I am in receipt of a letter which you addressed to Dr. J. Harvey Black, Secretary of the Association for the Study of Allergy. This association is no longer in existence, having been amalgamated with the Society for the Study of Asthma and Allied Conditions, in 1943, to form the present American Academy of Allergy, of which I am Secretary.

Upon receipt of your letter, I sent copies of it to all the members of the Executive Committee of the American Academy of Allergy. The committee members unanimously instructed me to assure you of our moral support and the deep interest of the Academy of Allergy in the movement which you are sponsoring.

Since advances in the field of Allergy depend so largely upon animal experimentation, it is inevitable that our society should want to support your efforts in every way. Therefore, please be assured that the American Academy of Allergy heartily endorses the work of the National Society for Medical Research.

Very truly yours,

KARL D. FIGLEY, Secretary.

Book Reviews

Allergia e Malattie Allergiche. Gianfranco Capuani, Torino, 1945, Minerva Medica, pp. 829, paper, illustrated.

This work by members of the faculty of medicine of Montevidio, Uruguay, represents The subject is approached from a broad viewpoint, wherein the fundamentals of allergy are discussed in detail and then each of its clinical expressions elaborated upon. It is documented by an extensive bibliography, international in scope, and it is of interest that where American references are cited, they are usually significant ones. The author's attitude is conservative. His training in medicine and pathology is expressed in a scholarly and objective presentation of his subject.

In the opinion of the reviewer, this work compares favorably with any that has appeared in recent years. It seems remarkable that the date of publication is 1945, when Italy was so depleted of material resources. The illustrations are more than adequate, and skin reactions are shown in color. The production of this work under the circumstances testifies to the fine spirit and courage of its author.

Alergia en la Practica Clinica. B. Varela Fuentes, P. P. Recarte, and A. Grana, Buenos Aires, 1946, Espasa Calpe, pp. 974, paper, illustrated.

This work by members of the faculty of medicine of Montevideo, Uruguay, represents a viewpoint shared by other South American authors. On the one hand it is more comprehensive than that of North American allergists. The allergy of tuberculosis, lymphogranuloma inguinale, and other infections including parasites is considered in detail. Allergy to physical agents and the role of histamine are elaborated upon. This is quite understandable, for the infections considered loom large in South America, and the brilliance of Rocha e Silva is reflected in serious interest in the role of histamine. All this makes interesting reading, but this reviewer is not convinced, probably because of his own lack of experience.

In contrast to this liberal viewpoint is a restricted one, wherein there is great emphasis on "Digestive Allergy." Foods are incriminated repeatedly for many clinical syndromes and are considered most important sources of allergy.

The remainder of the book consists of conventional material found in most textbooks.

What You Don't Know May Hurt You. J. A. Rudolph and H. N. Rose, Philadelphia, 1946, Dorrance & Company, Inc., pp. 138, illustrated.

This book was written to inform the public about allergy which turns out to be a dreadful disease. It may be responsible not only for what everyone knows but also for facial distortion with receding chin, poorly focused eyes, bronchial abscess, chronic heart trouble, stomach ulcers, convulsions (from eating animal crackers), and many other ills of the flesh. It is written in a facetious manner with caricatures as illustrations.

This is the sort of thing that hurts allergy badly in the minds of the profession and of the enlightened public. Although it was doubtless written with good intent, it is unfortunate that there can be no control over publications of this type.